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Health Assessment Document for 1,1,1-Trichloroethane (Methyl Chloroform)

Richard Carchman, et al

U.S. Environmental Protection Agency
Research Triangle Park, North Carolina

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16. ABSTRACT

The incidence of adverse health effects at low ambient air levels (approx. 100 ppt.) is unknown. Because methyl chloroform accumulates in the body, long-term exposure to even low ambient air levels might represent a health hazard. A no-observed-effect-level for long-term occupational exposure of humans to methyl chloroform is presently assumed to be around 53 ppm. At exposure levels around 1,000 ppm, inhalation produces cardiovascular effects in humans that include sensitization of the heart to spontaneous or catecholamine-provoked arrhythmias and hypotension.

Methyl chloroform has been demonstrated to have mutagenic activity in the Ames assay, with and without metabolic activation, and in cultured mammalian cell transformation systems. However, definitive evidence that it has carcinogenic potential has not been demonstrated in animal bioassays. While it may have teratogenic potential, limitations of the available data do not allow for a full assessment of its effects. Because of its lipophilic nature, methyl chloroform is expected to cross membrane barriers and diffuse into the brain and milk of nursing mothers, as well as into the fetus during pregnancy.

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HEALTH ASSESSMENT DOCUMENT
FOR
1,1,1-TRICHLOROETHANE
(METHYL CHLOROFORM)

Notice

This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
Environmental Criteria and Assessment Office (MD-52)

DATE November 16, 1982

SUBJECT Revised Draft of EPA OHEA Health Assessment
Document for Methyl Chloroform

FROM Lester D. Grant, Ph.D., Director Lester D. Grant
Environmental Criteria and Assessment Office (MD-52)

TO Dr. Roger McClellan, Chairman
Health Committee, EPA Science Advisory Board (SAB)

Attached please find a revised draft of the EPA (OHEA) Health Assessment Document for Methyl Chloroform earlier circulated as an External Review Draft (EPA-600/8-82-003; January, 1982) for public comment and SAB review.

The attached November, 1982, draft of the Methyl Chloroform Document incorporates revisions that take into account both: (1) public comments received on the earlier January, 1982, External Review Draft; and (2) recommendations provided by the SAB Health Committee under your Chairmanship in connection with the Committee's peer-review of the January draft at its recent September 28-29, 1982, public meeting in Washington.

The main revisions which have been incorporated into the attached November, 1982, draft include the following:

(1) The list of Authors and Reviewers (Pp. ix-xi) has been revised to identify clearly the individuals/groups responsible for preparation of specific chapters/sections of the document.

(2) The Summary and Conclusions (Chapter 1) materials have been revised to reflect changes in key information or conclusions presented in later, detailed chapters of the document. For example, the Summary and Conclusions discussion of the role of methyl chloroform in stratospheric O_3 perturbations has been changed in keeping with revisions made in later chapters to better reflect state-of-the-art knowledge concerning the subject, as characterized in the 1982 WMO and NRC(NAS) reports on stratospheric ozone perturbations by halocarbon compounds and other atmospheric pollutants. Additional revisions of these Summary and Conclusions materials (and pertinent later chapter text on the subject of stratospheric O_3 depletion) are planned to be incorporated into the final draft of this health assessment document. This will update even further the treatment of the subject in light of recently published (Owens, et al., September, 1982) or about-to-be published re-analyses that point toward lower likely overall rates of stratospheric O_3 depletion (if any at all) being associated with emissions of methyl chloroform or other halocarbons, when offsetting repletion of O_3 due to other

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air pollutants is taken into account. In addition, in the Summary and Conclusions chapter, the discussion of directly-induced health effects has been expanded to delineate the estimated NOEL range from the lowest observed effect levels for methyl chloroform based on presently available toxicological data; a table summarizing observed effect levels for single, short-term exposures has also been added to the Summary and Conclusions.

(3) Materials in Chapter 3 on nationwide emission levels for methyl chloroform have been updated to reflect the most recent, currently available information, as provided by Katz, et al. (1980) and Anderson, et al. (1980). The following additional, newly-available references have been added and discussed in Chapter 3:

Anderson, G. E., et al., 1980
Chian, E. S. K. and B. B. Ewing
Chow, C. S., 1981
Coniglio, W. A., et al., 1981
Derwent, R. G., 1982
Dilling, W. L., 1977
Fabian, P., et al., 1981
Hiatt, M. H., 1981
Krost, et al., 1982
Lionel, T., et al., 1981
Otson, R. and D. T. Williams, 1982
Pellizzari, E. D., 1982
Pellizzari, et al., 1982
Singh, et al., August 1982

(4) The chapter on metabolism and pharmacokinetics (Chapter 4) has been revised to reflect more appropriate terminology as discussed at the September 28-29 SAB meeting. Additional discussions have been incorporated on recent literature, including evaluation of the following studies:

Astrand, I., 1975
Caperos, et al., 1982
Filser, J. G. and H. M. Bolt, 1980
Filser, et al., 1982
Guillemin, M. and E. Guberan, 1982
Jakobson, et al., 1982
Leighty and Fentiman, 1981
Platt and Cockrill, 1969
Schumann, et al., 1982a
Schumann, et al., 1982b

(5) The information pertaining to neurotoxicology and behavioral toxicology, in Chapter 5, has been reviewed and critiqued by EPA's Health Effects Research Laboratory. A new subsection, 5.2.2 (written by that group) has been added, which incorporates revised discussion of the animal toxicology studies and appropriate conclusions.

Anderson, et al., 1980
Anderson, M. E., 1981a
Anderson, M. E., 1981b
Anderson, M. E., 1981c
Benignus and Muller, 1982
Carlson, G., 1981
deSerres, et al., 1981
Federal Register, December 16, 1977
Gocke, et al., 1981
Henschler, et al., 1980
Kronevi, et al., 1981
Lane, et al., 1982
Lee, et al., 1982
Mazaleski, 1979
Miyata, et al., 1981
Moser and Balster, 1982
Nestmann, et al., 1980
Riddle, et al., 1981
Topham, 1980
Woolverton and Balster, 1981

(6) The OHEA Carcinogen Assessment Group's discussion of carcinogenic aspects now appears in chapter format rather than as an appendix

to the document. This chapter has been revised to account for any newly-available, recently-published information. Similarly, material on mutagenicity aspects (prepared by the OHEA Reproductive Effects Assessment Group) is incorporated as a chapter and has been revised to take into account any newly-available recent literature and comments/recommendations derived from the peer-review discussions at the September 28-29 SAB Meeting.

We feel that the above main revisions and others incorporated into the attached draft adequately address the substantive issues raised by Public Comments or the SAB Health Committee in review of the earlier January, 1982, draft of the Methyl Chloroform document. We look forward to final closure by the Committee on the attached draft and wish to thank members of the Committee for their excellent and helpful recommendations concerning revision of the earlier draft reviewed by them.

Attachments

DISCLAIMER

The report is an external draft for review purposes only and does not constitute Agency policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

The Office of Health and Environmental Assessment has prepared this health assessment to serve as a "source document" for EPA use. The health assessment was originally developed for use by the Office of Air Quality Planning and Standards to support decision-making regarding possible regulation of methyl chloroform as a hazardous air pollutant. However, the scope of this document has since been expanded to address multimedia aspects.

In the development of the assessment document, the scientific literature has been inventoried, key studies have been critically evaluated and summary/conclusions have been prepared so that the chemical's toxicity and related characteristics are qualitatively identified. Observed effect levels and other measures of dose-response relationships are discussed, where appropriate, so that the nature of the adverse health responses are placed in perspective with observed environmental levels.

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The EPA Office of Health and Environment Assessment (OHEA) is responsible for the preparation of this health assessment document. The OHEA Environmental Criteria and Assessment Office (ECAP/RTP) had overall responsibility for coordination and direction of the document preparation and production effort (Mark M. Greenberg, Project Manager).

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1. SUMMARY AND CONCLUSIONS

1,1,1-Trichloroethane (methyl chloroform, MC) is a volatile (125 torr @ 25°C) chlorinated hydrocarbon compound which is manufactured and used in large quantities. It is not soluble to any appreciable extent in water. Since its commercial introduction in the mid-1900s, it has been used increasingly as an industrial solvent and in consumer products, such as spot removers. In recent years, the U.S. production of MC has grown significantly; production is estimated to have increased from 121,000 metric tons in 1970 to 325,000 metric tons in 1979. The compound is produced by three manufacturers that have a combined total annual production capacity of about 453,000 metric tons. the popularity of methyl chloroform is apparently due primarily to early studies which indicated that it had a very low toxicity in comparison to other halogenated hydrocarbon solvents with similar physical properties.

It is estimated that approximately 88 percent of the MC consumed (about 300,000 metric tons annually) in the United States is lost directly to the environment through dispersive use, largely by evaporation to the atmosphere. Three-quarters of the air emissions are attributed to metal cleaning operations which consume 66 percent of the total production. There are no known natural sources of MC. In addition to the workplace, MC has been detected in ambient (natural environment) air of a variety of urban and non-urban areas of the United States and other regions of the world. Based on available information, ambient air levels range from trace amounts to about 20 ppb (0.108 mg/m^3) for some large urban centers. Air samples from rural and remote areas are normally less than 100 parts per trillion (ppt). In surface ground waters and drinking waters, MC is generally found at levels near 1 ppb or less, although much higher levels have been reported in certain waste waters and specific instances of contamination of ground water.

Unlike chlorofluorocarbons, which are not known to be removed by mechanisms in the troposphere, MC is removed to a substantial extent through reaction with hydroxyl radicals. The tropospheric lifetime of MC is generally assumed to be within a range of 5 to 10 years in spite of the lack of scientific agreement on the global average concentration of hydroxyl radicals. It is estimated that this period of time allows about 15 percent of the MC emitted to survive tropospheric removal mechanisms and reach the stratosphere. The most recent data regarding tropospheric levels suggest that the average global tropospheric mixing ratio for MC is 0.18 ppb (9.7 X 10^{-4} mg/m^3). Chlorine atoms released from MC by photodissociation in the stratosphere participate in ozone (O_3) destruction pathways. Therefore, it is hypothesized that MC and other compounds that add to the atmospheric chlorine burden may contribute to the effects of global ozone depletion (if such occurs) on human health, i.e., an increased incidence of non-malignant forms of skin cancer due to increases in the amount of biologically-damaging radiation reaching the earth's surface. However, the extent to which stratospheric ozone is depleted by all halocarbons and the extent to which past, current and future emissions of MC contribute to this depletion can only be estimated by assessing all the reactions that are involved in O_3 formation and destruction via multiple pertubation simulations. It is not currently possible to verify stratospheric O_3 changes by direct measurement. If MC replaces other solvents in the future, or as new uses for MC are found, MC will necessarily play a more significant role in ozone photochemistry. Given a potential for adverse consequences for human health associated with decreases in stratospheric O_3, present and future emissions of MC should be carefully evaluated in the future in relation to its impact on this important component of the atmosphere.

With regard to direct health effects, cardiovascular effects have been observed in animals and humans at anesthetic levels of MC (10,000 to 50,000 ppm; 54,000 to 270,000 mg/m^3). At 1,000 ppm (5,400 mg/m^3), inhalation of MC has produced cardiovascular effects in humans that include sensitization of the heart to spontaneous or catecholamine-provoked arrhythmias and hypotension. This cardiovascular response is, in part, the result of MC's ability to depress the conduction system of the heart.

At lower concentrations of MC likely to be encountered in the workplace (TWA* = 350 ppm; 1,890 mg/m^3), the no-observed-effect level† (NOEL, 350 to 500 ppm; 1,890 to 2,700 mg/m^3) is a range in which odor is obvious but no significant abnormal blood chemistry or organ function tests have been noted. The main health effects observed at higher levels are neurological symptoms, which have been qualitatively diagnosed by subjects' impaired performance of clinical-level cognitive and manual tasks. In regard to still lower exposure levels, however, much more extensive human and laboratory animal data are needed before firm conclusions about low-level effects of MC can be drawn.

---

*TWA (Time Weighted Average): is defined as the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek to which nearly all workers may be exposed repeatedly, day after day, without adverse effect.

†NOEL: is defined as the lowest exposure level at which there are no statistically significant increases in frequency or severity of effects between the exposed population and its appropriate control.

The probability of adverse health effects resulting from low ambient air chronic exposure levels (~ 100 ppt) cannot be conclusively estimated, but the likelihood of such effects occurring appears to be extremely low based on presently available data. Specifically, a no-observed-effect-level (NOEL) for long-term exposure of humans to MC is estimated to be approximately 350 ppm (1,890 mg/m^3). This NOEL is many times higher than the highest levels of MC (20 ppb; 0.108 mg/m^3) measured in the ambient air of urban areas. Although a precise dose-response gradient of effects produced by MC exposure cannot be derived, it is possible to establish a less precise relationship between exposure and effects from a compilation of the human data available. The estimated relationship for acute effects of single short-term exposures is as follows:

> 5,000 ppm	onset of narcosis
1,900 to 2,650 ppm	lightheadedness, irritation of the throat
1,000 ppm	disturbance of equilibrium
350-500 ppm	slight changes in perception, obvious odor
100 ppm	apparent odor threshold

Based on the weight of available evidence, it can be concluded that commercially available samples of MC are weakly mutagenic to base-pair substitution strains of Salmonella under treatment conditions where precautions have been taken to prevent escape of MC vapors. However, adequate data are not available for reaching firm conclusions regarding the ability of MC to cause gene mutations in other organisms or other types of genetic damage. In order to determine conclusively the mutagenic potential of MC, pure MC should be tested in studies appropriately designed to ensure exposure of the indicator organisms. Since positive responses were obtained in the Salmonella assay, MC is judged to have mutagenic potential and a possible mutagenic effect in humans cannot be precluded. In studies conducted to date in rodent species, MC has not demonstrated any teratogenic potential. The extent to which any carcinogenic potential of MC might be realized is linked to biochemical mechanisms involved in its in vivo metabolism. Methyl chloroform may be biotransformed to "reactive intermediate" metabolites which might contribute to tissue and organ toxicities, as well as carcinogenesis. However, the evidence for "reactive intermediate" metabolites is fragmentary. Animal bioassays performed by the National Cancer Institute (NCI) and others have not provided definitive evidence of carcinogenicity, due to shortcomings of the studies. Thus, the carcinogenic potential of MC cannot be assessed until the results of long-term bioassays, some recently-completed, become available and are fully evaluated.

Like other halogenated hydrocarbon solvents, inhalation of MC is the most important and rapid route of absorption into the body. It is estimated that for an 8-hour exposure at the TWA (350 ppm; 1,890 mg/m^3), about 2 grams will be absorbed into the body of a normal 70 kg man. The total amount absorbed increases in direct proportion to inspired air concentration and to length of exposure and physical activity. However, at equilibrium, only approximately 30 percent of the inspired air concentration is retained. Because of its lipophilic nature, MC is expected to cross membrane barriers in the body and diffuse into the brain and the milk of nursing mothers, as well as into the fetus during pregnancy. There is strong evidence that MC will partition selectively into lipid-rich tissues upon chronic or long-term exposure to even low ambient air concentrations until a steady-state is reached. Methyl chloroform is metabolized in man to a very limited extent (about 6 percent or less of the total retained dose).

The primary route of elimination of MC is via the lungs. The only identified urinary metabolites are trichloroethanol and trichloroacetic acid. Metabolism of MC is enhanced by other chemicals and drugs such as phenobarbital. There is no information indicating that MC enhances its own metabolism.

The likelihood and extent to which adverse health effects could result is, in part, linked to biochemical mechanisms of MC metabolism in the liver. It is possible that MC may be biotransformed to "reactive intermediate" metabolites which may contribute to tissue and organ toxicities; however, the present evidence for reactive intermediate metabolites of MC is inconclusive.

Until there is considerably more information available on the biological effects of MC and its potential role in contributing to an increased incidence of skin cancer as a result of ozone depletion, a definitive evaluation of health hazards associated with its use in the workplace and its presence in the ambient environment is not possible.

2. INTRODUCTION

1,1,1-Trichloroethane (methyl chloroform, MC) belongs to a family of saturated chlorinated compounds widely used in industrial cold cleaning and vapor degreasing operations, in the synthesis of vinylidene chloride, and in consumer products. This document provides an evaluation of the health effects of MC and a review of the relevant available scientific literature. In order to provide a perspective in evaluating health effects associated with MC, this document contains background chapters relating to analytical methodologies, production, sources and emissions, and ambient* air concentrations.

Methyl chloroform is released into the ambient air as a result of evaporation during its production, storage, and manufacturing or during general consumer use. It is not known to be derived from natural sources. In recent years, attention has been focused upon the possible role of MC in multiple perturbations of stratospheric ozone. It has been hypothesized that stratospheric ozone depletion may indirectly result in increased ultraviolet radiation at the earth's surface, thereby contributing to an increased incidence of human skin cancer. MC is one of the many atmospheric pollutants the reactivity of which is sufficiently low to allow it to be transported to the stratosphere; its trophospheric lifetime is estimated to be 5 to 10 years. Concentrations of MC in ambient air sampled around the nation reflect both efforts in recent years to control emissions of it and transport and transformation processes in the atmosphere.

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*Ambient is used in this and other documents of this nature to refer to the environment and should not be construed to include indoor, including occupational, settings.

The published scientific literature on MC is limited in reference to its effects on humans. Because of the diverse uses of MC and the difficulty of identifying large cohort populations, there are relatively few epidemiological studies. What is known about the effects of MC has been primarily derived from studies involving individuals exposed occupationally or accidentally to MC. In such exposures, the concentrations of MC associated with adverse effects to human health were either unknown or far in excess of the concentrations measured in ambient air. Controlled exposure studies in humans have been carried out at TWA* concentrations (350 ppm; 1,890 mg/m^3) and have been directed toward elucidation of subjective response, CNS effects, and the pharmacokinetic parameters of MC exposure. These studies have established that vapor inhalation is the principal route by which MC enters into the body. It is widely distributed into all organ systems and is metabolized to a limited extent. MC is eliminated from the body primarily as the parent compound via the lungs, but metabolites are excreted mostly in the urine. Epidemiological studies provide some information about the impact of MC on human health, but it is necessary to rely on animal studies to assess any indications of potentially harmful effects for chronic low-level exposure. These studies are reviewed in chapters 4 and 5.

Of chief concern regarding the potential impact of MC on human health are: (1) narcosis effects associated with acute high-level exposures and (2) any mutagenic or carcinogenic effects potentially associated with chronic low-level exposures. This document reviews evidence regarding acute narcosis effects and, also, summarizes available mutagenicity evidence and peer-reviewed results of animal bioassay studies that relate to the carcinogenic potential of MC. A definitive evaluation of the carcinogenicity of MC is being deferred until the results of a recently-completed National Toxicology Program bioassay in rats and mice are published and undergo complete peer review.

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*TWA (Time Weighted Average): is defined as the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek to which nearly all workers may be exposed repeatedly, day after day, without adverse effect.

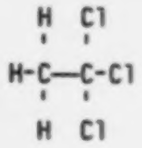
Permissible levels of MC in the working environment have been established in various countries. The U.S. Occupational Safety and Health Administration (OSHA) health standard requires that a worker's exposure to MC at no time exceed an 8 hr time-weighted average of 350 ppm (1,890 mg/m^3) in the workplace air in any work shift of a 40-hr week.

3. GENERAL BACKGROUND INFORMATION

3.1 CHEMICAL AND PHYSICAL PROPERTIES, ANALYTICAL METHODOLOGY

3.1.1 Chemical and Physical Properties

1,1,1-Trichloroethane (CH_3CCl_3), also called methyl chloroform (MC), is a colorless nonflammable liquid which has a characteristic odor. Its line formula is:



$$\begin{matrix} & H & & Cl & \\ & | & & | & \\ H- & C & — & C & -Cl \\ & | & & | & \\ & H & & Cl & \end{matrix}$$

Chemical Formula $C_2H_3Cl_3$

Chemical Abstracts Service Registry Number 71-55-6

Synonyms and Identifiers

Aerothene TT
Chloroethane NU
Chlorotene
Chlorothane NU
Chlorothene
Chlorothene NU
Chlorothene VG
Chlorten
Ethane, 1,1,1-Trichloro
Inhibisol
Methyl Chloroform
Methyltrichloromethane
NCI-C04626
Alpha-T
Trichloroethane
1,1,1-Trichloroethane
α-Trichloroethane

Table 3-1 shows some of its important chemical and physical properties.

TABLE 3-1. PHYSICAL PROPERTIES OF 1,1,1,-TRICHLOROETHANE

Solubility in water @ 25°C	0.44 gm/100gm
Boiling point @ 760 torr	74°C
Vapor pressure @ 20°C	100 torr
Vapor density (air = 1)	4.6
Molecular weight	133.41
1 ppm	5.4 mg/m^3

In the atmosphere, MC is subject to free radical attack and reaction with hydroxyl radicals is the principal way in which it is scavenged from the atmosphere. Photooxidation products of MC include hydrogen chloride, carbon oxides, phosgene, and acetyl chloride (Christiansen et al., 1972). The principal tropospheric photooxidation product has been reported to be trichloroacetaldehyde (U.S. Environmental Protection Agency, 1975). Data discussed in Section 3.3 indicate that MC is relatively stable in the troposphere and that significant amounts are conveyed to the stratosphere.

In water, methyl chloroform is slowly hydrolyzed to predominantly acetic and hydrochloric acids (Dilling et al., 1975). Dilling et al. (1975) reported a half-life of hydrolysis of 6 months at 25°C (dark reaction).

Anhydrous MC is generally noncorrosive, but in the presence of water it can react to form hydrochloric acid, which is corrosive of metals (Keil, 1979). The addition of epoxides can neutralize the generated acid (Keil, 1979). Anhydrous MC, when heated to 360° to 440°C, decomposes to 1,1-dichloroethylene and hydrogen chloride. When MC is heated in the presence of water at temperatures between 75° and 160°C, it decomposes to acetyl chloride, acetic acid, and acetic anhydride upon contact with metallic chlorides or sulfuric acid. Noweir et al. (1972) have observed that when MC comes in contact with iron, copper, zinc, or aluminum at elevated temperatures, phosgene is produced.

Bonse and Henschler (1976) have considered the general chemical reactivity of MC. By virtue of the electron-inductive effects of the chlorine substituents, destabilization occurs at the C-C bond. Radical reaction mechanisms would be favored as a result of the delocalization of the unpaired electron drawn from the C-C bond.

3.1.2 Analytical Methodology

To detect very low levels of methyl chloroform in ambient air, sophisticated analytical techniques have been employed. The two most generally useful methods for detection and analysis of MC have been gas chromatography with electron capture detection (GC-ECD) and gas chromatography-mass spectrometry (GC-MS). Both systems have a lower limit of detection on the order of a few parts per trillion (ppt). The utility of GC-ECD over GC-MS is that it can be used in the field to provide nearly continuous measurements through intermittent sampling (every 15 to 20 minutes).

In a comparison between GC-ECD and GC-MS, Cronn et al. (1976) judged GC-ECD to be superior in precision. Standards for four halocarbon compounds, measured by GC-ECD, had coefficients of variation ranging from 0.5 to 3.5 percent. Of 11 halocarbon compounds measured by GC-MS, coefficients of variation ranged from 4 to 19 percent. Temperature programming or isothermal operation of the gas chromatograph yielded comparable results (Cronn et al., 1977). The precision with temperature-programming was 4.3 percent versus 3.5 percent with isothermal operation for MC.

A close agreement between the levels of MC and other halocarbons detected by both GC-ECD and GC-MS (on the same ambient air samples) was obtained by Russell and Shadoff (1977). A difference of 10 ppt was reported between the systems. Air samples were sorbed onto Porapak N porous polymer and desorbed onto the column by heating the collection tube rapidly to 200°C. Ambient air mixing ratios measured by this method were in the range of 90 to 110 ppt.

The electron capture detector, as well as the mass spectrometer in the selective ion monitoring mode (Cronn and Harsch, 1979a; Pellizzari, 1974), is specific in the detection and quantitation of many halogenated hydrocarbons, whereas nonhalogenated hydrocarbons are not detected. Thus, a high background level of hydrocarbons in ambient air samples does not preclude analysis of trace quantities of MC. In the electron capture detector, MC is ionized by primary electrons released from an internal radioactive source. The net result is removal of electrons from the gaseous mixture with substitution by negative ions of greater mass. The measured effect is a net decrease in ion current because the mobility of the ions is less than that of the electrons.

Samples of tropospheric air were analyzed by Cronn and coworkers (1977) both by preconcentrating the samples according to the method of Rasmussen et al. (1977) and by direct injection. The detection limit was 3 ppt. The precision of the method using preconcentration was ±4 percent. The internal consistency between direct GC-ECD analysis of MC and using the preconcentration method was reported to be good (Cronn et al., 1977).

A detection limit of 2 ppt for MC was achieved by Harsch and Cronn (1978) with a low pressure sample-transfer technique. Precision was ±7 percent with the Rasmussen et al. (1977) preconcentration technique. Calibration was accomplished by use of secondary standards that were compared to static dilutions of pure and commercially prepared mixtures of MC (10 ppm) in helium. Robinson (1978) reported a detection limit of 6 ppt with a precision of ±4.2 percent with secondary standards in a system using dual GC-ECD.

Pellizzari and Bunch (1979) reported an estimated detection limit of ~ 12.45 ppt (66 x 10^{-6} mg/m^3) using high resolution gas chromatography/mass spectrometry. The detection limit was calculated on the basis of the breakthrough volume for 2.2 grams of Tenax GC, at 21°C. The accuracy of analysis was reported at ± 30 percent. Similar results were also reported by Krost et al.(1982). Sources of error are discussed in section 3.1.2.1.

The relatively high volatility of MC was used to advantage by Piet et al. (1978) in measuring the content of MC in water samples. A direct headspace method was used with MC volatilizing into the air above the surface of the water sample in a sealed container. A GC-ECD system was used for separation and quantitation. The systematic error of the method was reported to be less than 5 percent. The detection limit for MC was 0.05 µg per liter. The OV 225 capillary GC column provided good separation of MC from CCl_4.

Otson and Williams (1982) have described a modified purge and trap technique for evaluation of volatile organic pollutants in water. The detection limits reported for MC was 0.5 µg/l, using either flame ionization detection or electron capture. Tenax GC was used as packing for the combined trap/chromatographic column. Purging efficiency was close to 100 percent.

Lionel et al. (1981) provided additional evidence that aeration can be used successfully to purge compounds such as MC from water. Experimental techniques suggest that at appropriate air flow, over 90 percent of MC can be purged from water.

The purging efficiency from samples of sediment and fish tissue spiked with MC was investigated by Hiatt (1981). Samples were sonicated, frozen, and then subjected to three analytical methods: vacuum extraction, direct purge and trap of diluted sample, and modified purge and trap with thermal desorption. For MC, vacuum extraction appeared to result in the highest recovery. These preliminary data do suggest that vacuum extraction has application to environmental analysis of similar samples.

The purgeability of MC from mother's milk has been evaluated by Pellizzari et al. (1982). Samples were collected from donors in four urban areas. Milk was manually expressed into bottles that were capped, then frozen. All volatile compounds were recovered by warming the milk and purging with helium. Vapors were then trapped on a Tenax cartridge, followed by thermal desorption. In the eight milk samples analyzed, MC was detected in 8 of 12 total samples analyzed.

3.1.2.1 Sampling and Sources of Error--The National Academy of Sciences (1978) has reviewed common approaches used to sample ambient air for trace gas analysis. These approaches include:

1. Ambient pressure samples. An evacuated chamber is opened and allowed to fill until it has reached ambient pressure at the sampling location. If filling is conducted at high altitude, contamination of the low pressure sample is likely when samples are returned to ground level.

2. Pump pressure samples. A mechanical pump is used to fill a stainless steel or glass container to a positive pressure relative to the surrounding atmosphere.

3. Adsorption on molecular sieves, activated charcoal, or other materials. Sorbents that have been used to collect MC include Porapak Q, Tenax GC, and Chromosorbs 101, 102, and 103.

4. Cryogenic sampling. Air samples are transferred to a loop held at the temperature of liquid oxygen. Components, including MC, are concentrated by freezeout while other gases (oxygen, nitrogen) pass through.

In the analysis of whole air samples of compounds such as MC, which are present in ambient air in the ppt range, small uncontrolled errors in the system could result in inaccurate results. Errors in the analysis can occur during sampling, in the gas chromatograph, in the EC detector, and in calibration of the instruments.

Rasmussen and Khalil (1981) reported that, in an interlaboratory comparison of two samples of MC in ambient air, a majority of the 19 participating laboratories reported values lower than those determined by the authors. It was concluded that common standards are needed if atmospheric measurements from different laboratories are to be pooled.

Singh and coworkers (1978a) used electrochemically-polished stainless steel sampling vessels. The sampling vessels were flushed with ultra-pure helium until background contamination was reduced to less than 2 to 3 percent of the expected background concentration of a given trace constituent. Cronn and coworkers similarly employed electropolished stainless steel containers whose interior surfaces had been passivated by electropolishing (Cronn and Robinson, 1978; Cronn et al., 1976; 1977).

Harsch and Cronn (1978) have evaluated sample transfer techniques. Most analytical procedures involve the collection of pressurized air samples. Sample transfer under positive pressure minimizes serious contamination possibilities posed by laboratory air containing many times the ambient mixing ratios of most halocarbons. However, collection of low pressure samples, such as stratospheric air samples, is a specialized situation in which careful precautions against sample contamination are necessary. A technique applicable to collection of whole air samples at altitudes up to 21 kilometers showed a 7 percent standard deviation when the MC mixing ratio was 105 ppt (Harsch and Cronn, 1978). Electropolished sampling bottles were evacuated to 30 microns prior to sample collection. Transfer of contents to a freezeout loop (Rasmussen et al., 1977) (immersed in liquid O_2) was made by vacuum assist. Preconcentration was followed by injection onto a temperature-programmed column. The detection limit for MC with the GC-ECD procedure was 2 ppt. To minimize the number of potential sources of leaks, system components were silver soldered. The technique was applicable when gross halocarbon levels were not present in laboratory air. However, it was noted that if laboratory air contained ppb levels of halocarbons, high-boiling halocarbons were adsorbed onto the surfaces of the fittings of the sampling containers and associated plumbing during times when the system was exposed to laboratory air.

The EC detector can be a source of error because water vapor and oxygen may cause reduced sensitivity for certain halocarbons. Lillian and Singh (1974) used an ascarite trap between the GC column and the detector to absorb sample moisture. Carrier gas for the GC is purified by passage through traps containing activated charcoal, anhydrous calcium sulfate, and an ascarite or molecular sieve (Cronn, 1980). Oxygen contamination in the detector can be minimized by preconcentration of air samples on porous polymers (Russell and Shadoff, 1977). Significant oxygen contamination is often caused by fitting leaks in the GC rather than by carrier gas contamination.

A freezeout concentration method was employed by Rasmussen et al. (1977) to determine atmospheric levels of MC in the presence of other trace vapors. The detection limit of MC was reported to be 0.8 ppt for 500 ml aliquots of ambient air when measured by GC-ECD. Precision was 4.3 percent. Standards were prepared by static dilutions in helium. During the procedure, the oven of the GC was cooled to -10°C. When freezeout was complete, the loop containing the concentrated air sample was immersed in heated water and the carrier gas swept the contents of the sample loop onto the column.

Pellizzari and Bunch (1979) reported the use of Tenax GC, a porous polymer based on 2,6-diphenyl-p-phenylene oxide, to absorb MC from ambient air. Recovery was made by thermal desorption and helium purging into a freezeout trap. Included among the inherent analytical errors were (1) the ability to accurately determine the breakthrough volume, (2) the percent recovery from the sampling cartridge after a period of storage, and (3) the reproducibility of thermal desorption from the cartridge and its introduction into the analytical system. To minimize loss of sample, cartridge samplers should be enclosed in cartridge holders and placed in a second container that can be sealed, protected from light, and stored at 0°C. In an analytical system using Tenax GC as the absorbent, Pellizzari and coworkers (Krost et al., 1982) reported a detection limit for MC of 12.4 ppt (6.7×10^{-5} mg/m^3). Analysis of the breakthrough volumes at various temperatures suggests that Tenax GC is not a particularly effective absorbent for MC.

3.1.2.2 Calibration--In general, calibration of the instrumentation for GC-ECD analysis of methyl chloroform has involved static, multiple dilutions of pure material in the ppm range to ppt levels (Cronn et al., 1976; 1977; Harsch and Cronn, 1978; Lillian and Singh, 1974; Singh et al., 1977a). Singh et al. (1977b) have cautioned that, in some cases, multiple dilutions of materials to ppt levels are tedious and prone to inaccuracies. Calibration problems were cited by The World Meteorological Organization (1982) as a factor responsible for the discrepancies in tropospheric measurements by different investigators. In order to overcome the difficulties in generating low-ppb primary standards of MC, Singh et al., (1981) has reported that permeation tubes offer the most accurate means. Permeation tubes were conditioned for at least two weeks and, during standard generation, were kept in holders maintained at 70 ± 0.1°C. Error in the permeation rate (980 mg/min) was ± 15 percent. A reproducible means of generating low-ppb primary standards was judged essential since there are considerable difficulties in storing long-term secondary standards. Various investigators have used GC-ECD systems to quantitate MC in ambient air samples (Cronn et al., 1976; 1977; Lillian and Singh, 1974; Rasmussen et al., 1977; Singh et al., 1977c). An interlaboratory calibration (Cronn et al., 1976) of six real ambient air samples gave a precision (percent standard deviation) of 11.4 ppt. A similar comparison calibration was reported by Singh et al., (1981).

Rasmussen and Khalil (1981) reported that primary standards of MC (~ 139 and 52 ppt) remained stable for up to about one year, even though the pressure in the master tanks had decreased significantly. More recently, Rasmussen and Khalil (1982) have found MC to be stable up to 2 years in internally passivated (SUMMA®) stainless steel flasks.

Because the ionization efficiency of MC in the EC detector is only 20 percent, use of dual EC detectors in series have been used to achieve higher accuracy (Lillian and Singh, 1974). The dual detection system, as employed by Singh et al. (1977c), enables MC to be quantitated coulometrically according to the following equation:

$$\text{Coulombs} = 96{,}500\ pW;$$

where

p = ionization efficiency

and W = moles of compound

Determination of the ionization efficiency can be made by use of the following expression which relates p to the signals (X_1 and X_2) of two identical EC detectors in series:

$$p = 1 - \frac{X_2}{X_1}$$

$$X_1 = 96{,}500\ pW$$

$$X_2 = p\ (96{,}500W - 96{,}500\ pW)$$

The ionization efficiency should be determined for the operating conditions and once established, can be used in the coulometric calibration.

The accuracy of the GC-ECD approach has been reported by Singh (1977a) to be better than 10 percent for compounds such as MC that have ambient air mixing ratios of 20 ppt or greater. An overall system accuracy of ± 10 percent was reported by Singh et al. (1977a) in analyses of MC in ambient air samples. Two gas chromatographs, each equipped with two EC detectors, were employed. An ascarite trap was placed between the GC column and the EC detector to prevent moisture interference. Precision was reported to be better than 5 percent and instruments were calibrated using multiple dilutions of pure material. Singh et al., (1981) recently reported linearity of dual frequency-modulated ECD's over a wide concentration range for MC, down to low-ppt levels.

3.1.2.3 Standard Methods--The analytical method S335, suggested by NIOSH for organic solvents in air, utilizes adsorption on charcoal followed by desorption with carbon disulfide. The resulting effluent is analyzed by gas chromatography. This method was recommended for the range 96 to 405 ppm. Interferences are minimal and those that do occur can be eliminated by altering chromatographic conditions. However, one disadvantage is that the charcoal may suffer breakthrough, thus limiting the amount of air that can be sampled. This can be predicted, however, and multiple tubes can be used. Tubes could also be replaced at predetermined frequencies after shorter sampling periods to avoid breakthrough.

3.2 PRODUCTION, USE, AND EMISSIONS

Methyl chloroform is principally used for the cold cleaning and vapor degreasing of fabricated metal parts. Because of its volatility and dispersive use pattern, much of the MC produced worldwide is emitted into the atmosphere. There are no identified natural sources of emissions. Once in the atmosphere, MC is subject to atmospheric transport and transformation. To better assess the effects of present and future emissions of MC on human health, this section profiles MC production, usage, and emissions.

3.2.1 Production

Methyl chloroform is produced by several manufacturing processes (Jordan, 1979; Lowenheim and Moran, 1975; U.S. Environmental Protection Agency, 1979b):

1. Hydrochlorination of 1,1-dichloroethylene (vinylidene chloride)

$$CH_2 = CCl_2 + HCl \xrightarrow{FeCl_3} CH_3CCl_3$$

2. Hydrochlorination of vinyl chloride

$$CH_2 = CHCl + HCl \xrightarrow{FeCl_3} CH_3CHCl_2$$

$$CH_3CHCl_2 \xrightarrow[Cl_2]{400^\circ C} CH_3CCl_3 + HCl$$

3. Chlorination of ethane

$$CH_3CH_3 + 3Cl_2 \xrightarrow{370^\circ \text{ to } 480^\circ C} CH_3CCl_3 + 3HCl + \text{byproducts}$$

In order to prevent catalyst deactivation, hydrochlorination reactions should be anhydrous (Jorden, 1979). Temperature control of thermal reactors for chlorination must be maintained to ensure MC stability (Jordan, 1979). In reaction (3) above, ethyl chloride and vinylidene chloride are byproducts. Increased yields of MC can be obtained through recycling of these byproducts.

In 1975, over 60 percent of the U.S. production of MC was derived from the hydrochlorination of vinyl chloride; derivation from vinylidene chloride accounted for 30 percent (Lowenheim and Moran, 1975).

In 1977, the U.S. production figure for MC was 288,565 metric tons (U.S. Environmental Protection Agency, 1979b; U.S. International Trade Commission, 1977). The major producers and their production capacities for 1977 are shown in Table 3-2. Quoting production estimates supplied by Dow Chemical U.S.A., Singh and coworkers (1979a) reported that production of the chlorocarbon has been increasing and, in recent years, this increase has been at the annual rate of 12 percent. Estimates did not take into account production in the

TABLE 3-2. MAJOR PRODUCERS OF METHYL CHLOROFORM. (Cogswell, 1978)

Organization	1978	Capacity (Metric Tons) 1982*
Dow Chemical, Freeport, TX	204,000	204,500
PPG Industries, Inc., Lake Charles, LA	79,000	159,000
Vulcan Materials Co., Geismar, LA	29,000	90,000

*These capacity estimates were provided in the 27 September 1982 Chemical Marketing Reporter and included production units on standby.

Soviet Union and other eastern European countries. The Dow Chemical estimate for global production in 1977 was 470,000 metric tons. The annual production growth rate through 1977 was reported to be 7 to 10 percent by trade sources (Chemical and Engineering News, 1979). Future growth in production depends on the status of other chlorinated solvents under regulation for which MC may be substituted and upon economic conditions.

3.2.2 Usage

In 1975, cold cleaning and vapor degreasing operations accounted for 75 percent of the total end use of MC. Approximately 12 percent was used in the synthesis of vinylidene chloride (Lowenheim and Moran, 1975). Use in metal cleaning operations was reported to total 67 percent of 1977 production (Cogswell, 1978).

MC is also used as a solvent in adhesive formulations, as a spot remover, as a film cleaner, and as an additive in metal cutting oils (Jordan, 1979; Keil, 1979; Lowenheim and Moran, 1975). Stabilizers used in MC are shown in Table 3-3 and protect it in the following ways (Jordan, 1979): (1) prevent or retard oxidation, (2) chelate metal ions, (3) scavenge HCl, and (4) passivate metal surfaces. Vapor degreasing grades of MC contain 3 to 7 percent (w/w) stabilizers and additives (Jordan, 1979); principal stabilizers include nitromethane, 1,3-dioxolane, 1,4-dioxane, butylene oxide, sec-butyl alcohol, isobutyl alcohol, N-methylpyrrole, and toluene (Jordan, 1979). In film cleaning applications, a low concentration of alcohol is used as a stabilizer (Jordan, 1979).

SRI International reported that between 11,000 and 13,000 metric tons of MC are used annually in personal care products (Cogswell, 1978). Expected growth in this area was reported to be 15 to 20 percent annually (Cogswell, 1978).

3.2.3 Emissions

Emissions of MC arise during primary and end product production, during dispersive use applications, from storage containers, and during disposal of waste materials.

Singh et al. (1979c) have estimated global emissions in 1977 at 95 percent of the 300,000 metric tons produced. Lovelock (1977a) estimated that 500,000 metric tons were released globally in 1975. The estimate of the global emissions rate in 1976 by the National Research Council (1979) was about 439,000

TABLE 3-3. STABILIZERS USED IN METHYL CHLOROFORM FORMULATIONS
(Jordan, 1979)

1,4 dioxane*
1,3-dioxolane*
butylene oxide*
epichlorohydrin
methyl ethyl ketone*
sec-butyl alcohol
isobutyl alcohol*
ethyl acetate
N-methylpyrrole
ter-amylphenol
hydroquinone monomethyl-ether
methylal
ethylene glycol mono and dialkyl ethers
methyl butynol
acrylonitrile
β-ethoxypropionitrile
diallylamine
diisopropylamine
acetaldoxime
nitromethane
nitroethane
N-methylmorpholine
Thymol

*Most commonly used commercial stabilizers

metric tons. The WMO (World Meteorological Organization, 1982), using data reported by Neely and Agin (U.S. E.P.A., 1980), estimated current global annual releases at 476,000 metric tons.According to McCarthy (1975), almost all the MC produced is eventually released to the atmosphere.

Recent estimates in a report prepared for the U.S. Environmental Protection Agency, Office of Toxic Substances, placed 1978 nationwide emission losses to air at 214,000 metric tons (Katz et al., 1980). A slightly higher rate (245,000 metric tons) for nationwide emissions from all sources for 1978 was reported by Anderson et al. (1980) in a study prepared for the U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. Emission estimates by sources category are shown in Table 3-4.

Based on annual measurements of global MC since 1975, Rasmussen et al. (1981) and Khalil and Rasmussen (1981) have determined that emissions of MC since 1974 have increased at an exponential rate of 8 percent per year. This is somewhat less than half the previous rate. The average rate of accumulation since 1975, based on the exponential equation $^{1}/_{C}\ ^{dC}/_{dt} = Bt$ and global emissions data, was calculated at 12.4 ± 1.5 percent per year.

TABLE 3-4. 1978 EMISSION LOSSES TO AIR

Source	1978 emission losses to air in million pounds (kkg) and percentage of total released to air		
Production			
1. From Vinyl Chloride	0.21	(95)	0.04%
2. From Vinylidene Chloride	0.15	(67)	0.03%
3. From Ethane	0.03	(14)	0.01%
Metal Cleaning	351.70	(159,500)	75%
Aerosols	39.90	(18,100)	8%
Adhesives	38.37	(17,400)	8%
Textiles	6.44	(2,920)	1%
Paints	10.91	(4,950)	2%
Inks	6.13	(2,780)	1%
Drain Cleaners	0.61	(278)	0.1%
Pharmaceuticals	0.27	(124)	0.06%
Film Cleaning	0.48	(218)	0.1%
Leather Tanning	0.23	(104)	0.05%
Catalyst Preparation	0.06	(28)	0.01%
Miscellaneous	14.82	(16,730)	3%
Total released to the air*	470	(213,300)	(100%)

*An additional 63 million pounds (28,602 kkg) are released to the environment via solid waste and water.

Adapted from Katz et al. (1980).

3.3. ATMOSPHERIC TRANSPORT, TRANSFORMATION AND FATE

The potential for ambient air mixing ratios of MC that should be considered to determine if MC poses a hazard to human health is influenced by the many processes that occur in the troposphere and stratosphere. Such processes include: transformation of MC into other potentially harmful atmospheric components; stability of such components; urban transport; tropospheric chemical reactivity; and diffusion into the stratosphere where MC participates in ozone (O_3) perturbation reactions.

3.3.1 Tropospheric Removal Mechanisms and Residence Time

Scientists generally agree that the longer the tropospheric residence time for a chemical species, the greater the likelihood of diffusion into the stratosphere. Determination of the residence time of MC and its loading of the global troposphere has long been a focus of research interest.

Prior to 1977, it was commonly believed that the residence time (i.e. the average time between release to and removal from the atmosphere) was in the range of 1 to 2 years (National Research Council, 1976). This residence time was derived from estimates of global average hydroxyl radical (OH) levels in the range of 10×10^5 to 30×10^5 molecules cm^3. It is important to note that reaction with OH is the principal tropospheric removal mechanism by which many compounds, including MC, are scavenged from the troposphere.

More recent modeling estimates of the loading of the troposphere by MC have led to refined estimates of OH mixing ratios and thus, suggest that the residence time of MC is more likely to be in the range of 5 to 12 years. Campbell (U.S. Environmental Protection Agency, 1980) calculated a mean atmospheric lifetime of 6.4 years based on oxidation by OH as a function of altitude and latitude.

Using reaction rates current for 1981, Logan et al. (1981) calculated a global lifetime of 5 years, by modeling MC mixing ratios over time and latitude and with altitude profiles of OH averaged over an annual cycle. The model results agree with those of Campbell (U.S. Environmental Protection Agency, 1980) in that MC removal is particularly sensitive to OH levels in the tropics, a region that accounts for about 70 percent of the global sink. Approximately 50 percent of the global sink is calculated over the tropical ocean. It was emphasized that one-dimensional models are inappropriate for calculating the lifetime of a compound such as MC. The model of Logan et al. (1981) calculated a mean OH level in the nothern hemisphere of 1×10^6 molecules/ cm^3. This is somewhat higher than the earlier estimates (2.5×10^5 per cm^3) calculated by Crutzen and Fishman (1977).

Derwent and Eggleton (1981), using a two-dimensional model, calculated a global lifetime of 4.8 years. Derwent (1982) has recently evaluated global, hemispheric, and one-dimensional models in comparison to a two-dimensional model. This report discusses the limitations and strengths of the various types of models used to estimate residence time and thus, the inherent differences between models in relation to estimates of stratospheric ozone changes. Methyl chloroform was one of three halocarbons chosen for the evaluation. It was concluded that the simpler model, with averaged chemical reaction rates and parameterization of transport processes, tend to under- or overestimate OH oxidation thus leading to errors in calculation of residence time. With respect to MC, however, both one- and two-dimensional models are in agreement with respect to atmospheric lifetime, 4.3 and 4.8 years, respectively. In contrast, hemispheric and global models yielded a lifetime of 8.9 years.

Singh and coworkers (1979b) found that field measurements support a 6 to 8 year global average residence time. Earlier, Singh et al. (1977a, 1977b) computed a global average residence time between 8 and 11 years, based upon the observed tropospheric distribution of MC and the rate of reaction with OH accepted at the time. Estimates from a number of other investigators, using different approaches, are consistent with a 5 to 12 year range (Altshuller, 1980; Chang and Penner, 1978; Lovelock (1977b).

The World Meteorological Organization (1982) recently reviewed the data base and found that, given the uncertainties in release rates and absolute concentrations of MC as discussed by Logan et al. (1981), the current mixing ratios observed for MC appear to be consistent with a lifetime of 5 to 10 years and with a globally averaged OH mixing ratio of about 7×10^5 molecules cm^3. This estimate was, in part, based on the redetermination of the rate constant for reaction of OH with MC by Kurylo et al. (1979) and Jeong and Kaufman (1979). The lack of knowledge concerning MC emissions from Eastern Bloc countries was also a factor that had been considered. Since OH distribution has only been estimated through the use of models, estimates for the atmosphereic lifetime of MC should be viewed cautiously.

Support for this estimate by the World Meteorological Organization can be seen in the data of Rasmussen and Khalil (1981b). These investigators reported that tropospheric measurements of MC made at six locations in the Northern and Southern hemispheres, between January 1979 and June 1980, were consistent with a lifetime in the range of 6 to 10 years. Average concentrations over both hemispheres were calculated from latitudinal profiles.

In conclusion, the estimates of the atmospheric lifetime of MC, as determined by reaction with OH, should be viewed cautiously given the limitations and uncertainties inherent in the various models. However, unless new information is forthcoming, the estimate of 5 to 10 years is consistent with the state-of-the-art knowledge of the troposphere.

3.3.2 Impact Upon the Ozone Layer

The National Research Council (1982), drawing upon the data base developed by the World Meteorological Organization (WMO, 1982), recognizes MC to have the potential to perturb stratospheric O_3 levels. This potential was not expressed in quantitative terms as had been done for the two principal chlorofluorocarbons believed to be the most important, namely, dichlorofluoromethane and trichlorofluormethane (CF_2Cl_2 and $CFCl_3$). The Council has stated that "The abundance of ozone in the stratosphere is determined by a dynamic balance among processes that produce and destroy it and transport it to the troposphere." Thus, the actual role of MC in stratospheric processes can best be elucidated through an examination of multiple perturbation scenarios involving all the known key contributory factors (National Research Council, 1982). The potential of MC, however, can be examined in a context apart from other perturbation processes. In this manner, important information concerning the atmospheric chemistry of MC can be used to develop more representative multiple perturbation simulations. The development of such models has been recommended by the Council to describe the combined effects of all relevant compounds on stratospheric O_3.

A tropospheric lifetime of 5 to 10 years for MC, as estimated by the WMO (World Meteorological Organization, 1982) suggests that a portion of the amount of MC released to the atmosphere reaches the stratosphere. Singh et al. (1982) have estimated that as much as 15 percent of the MC released enters the stratosphere. The National Research Council (1979a), using 1976 global release rates, estimated that about 12 percent reaches the stratosphere. Photodestruction of MC in the stratosphere would increase the atomic chlorine burden, thus accelerating O_3 destruction. Preliminary information reported by Fabian et al. (1981) suggests that MC is rapidly decomposed in the stratosphere. This mixing ratio profile awaits verification. Reduced O_3 concentrations associated with MC photodestruction could result from the following reaction mechanisms:

$$CH_3CCl_3 \xrightarrow{h\nu} CH_3CCl_2\cdot + Cl\cdot \qquad (1)$$

$$Cl\cdot + O_3 \longrightarrow ClO + O_2 \qquad (2)$$

$$ClO\cdot + O \longrightarrow Cl\cdot + O_2 \qquad (3)$$

$$ClO\cdot + NO \longrightarrow Cl\cdot + NO_2 \qquad (4)$$

The atomic chlorine produced in reaction (1) would react with O_3 to yield chlorine oxide. The subsequent chain reaction, if not counterbalanced, could result in a continual depletion of O_3.

The modelling results shown in Table 3-5 indicate the efficiency of MC to reduce O_3 relative to other stratospherically important compounds (U.S. Environmental Protection Agency, 1980). It must be noted that such results do not take into multiple perturbations that occur, some of which could offset the calculated effects of MC.

The World Meteorological Organization (1982), calculated an estimated steady-state depletion of the total O_3 column due to only MC of 0.8 percent. This estimate included an assumption of continued release at the current estimated emissions rate for MC and relied upon the one-dimensional model of the Lawrence Livermore Laboratory (Wuebbles and Chang, 1981) that incorporated revised reaction rate kinetics. It should be noted that other scenarious reported by the WMO, involving other reactive species, did not show a calculated net reduction in total column O_3.

Although a variety of scenarios involving multiple perturbations have been evaluated by the WMO (1982), it is difficult to assess with confidence the actual effect of MC in quantitative terms. Among the confounding factors are the uncertainties and limitations of the models and the complexity of rapidly-changing knowledge in atmospheric chemistry. An evaluation of the impact of MC upon stratospheric O_3 must take into account all factors affecting stratospheric processes if realistic estimates of O_3 depletion are to be made.

3.3.3 Laboratory Studies

In experiments designed to characterize the UV absorption spectrum for MC in the wavelength and pressure ranges associated with the stratosphere, Vanlaethem-Meurée et al. (1979) found that photo-dissociation was the dominant sink process at altitudes above 25 kilometers.

TABLE 3-5. RELATIVE EFFICIENCY OF HALOCARBONS IN REDUCING STRATOSPHERIC OZONE
(U.S. Environmental Protection Agency, 1980)

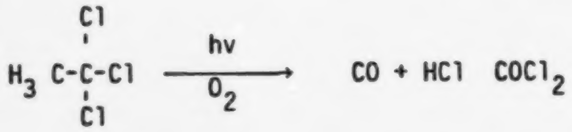
Compound	Percent ozone depletion after 320 years*
CFC-11	-10.7
CFC-12	-8.5
CFC-113	-8.25
CFC-114	-5.38
MC	-0.93[a]
	-1.6[b]

*production rate assumed, for each species individually, at 1,000 million pounds annually

[a] based on 4.5 year lifetime

[b] based on 9 year lifetime

In Spence and Hanst's (1978) photooxidation studies, when MC was irradiated at maximum intensities of 3100 Å and 3650 Å, one-fifth of the initial amount (10 ppm) was consumed after 6 minutes. The principal products observed were carbon monoxide (1.5 ppm), hydrochloric acid (6 ppm), and phosgene (2 ppm):



$$H_3\ C\text{-}\overset{Cl}{\underset{Cl}{C}}\text{-}Cl \xrightarrow[O_2]{hv} CO + HCl \quad COCl_2$$

The recent reaction rate studies, involving MC and OH, by Jeong and Kaufman (1981) and by Kurylo et al. (1981), indicate that the rate of this key reaction is slower and more temperature sensitive than previously had been indicated. Jeong and Kaufman (1981) measured reaction rates using the discharge-flow method and MC which had been extensively purified. A reaction rate at

293°K was determined at $1.06 \pm 0.09 \times 10^{-14}$ cm^3 sec^{-1}. The Arrhenius expression, within 95 percent confidence limits but not including systematic errors, was $5.49 \pm 1.40 \times 10^{-12}$ exp [- (1832 ± 98/T] cm^3 sec^{-1}. The authors indicated that the most recent rate (at 298°K) reported by JPL (Jet Propulsion Laboratory, 1979), 1.9×10^{-14} cm^3 sec^1 is too high by a factor of about 1.7 at this temperature, and by a factor of 1.9 at 265°K, the temperature used by Singh (1977) in deriving average OH concentrations.

The Arrhenius expression determined by Kurylo et al., (1979) was in close agreement with that determined by Jeong and Kaufman (1981). Kurylo et al. (1979) used the flash-photolysis method and also extensively purified the MC prior to use.

3.4 MIXING RATIOS IN THE ATMOSPHERE

Modeling approaches for reconciling emissions of MC to ambient air mixing ratios have implied low (3×10^5 to 6×10^5 molecules cm^{-3}) atmospheric levels of hydroxyl radicals (OH), the principal scavenging species for MC. If verified, these OH levels would strongly suggest that MC and many other chemical species have a tropospheric lifetime sufficiently long to allow their significant transport to the stratosphere. These models, however, have relied on point measurements of MC mixing ratios determined at disparate sites, primarily in the northern hemisphere. Before 1977, reliable estimates of globally averaged MC concentration were not available. Recent measurements, however, indicate that the global average concentration is consistent with a long (5 to 10 years) tropospheric lifetime.

3.4.1 Global Atmospheric Distributions

The global average background mixing ratio of MC has been determined by several laboratories, including SRI International and Washington State University. The field studies of Singh and co-workers at SRI have been reported in a number of publications (Singh, 1977a; Singh et al., 1977c; 1978a; 1978b; 1978c; 1979a; 1981). The global average for late 1977 was reported as 95 ppt (Singh et al., 1979a). This average was derived from measurements made in the northern (average = 113 ppt) and southern (average = 77 ppt) hemispheres. Based on data collected at latitudes 30°N to 40°N from 1975 to 1978, MC presence in the atmosphere was increasing at the rate of 15 ppt (or 17 percent) per year, during this time period.

Field studies by Singh et al. (1979a) were conducted during two oceanographic cruises between latitudes 64°N and 40°S (15 September to 30 October 1977; 20 November to 13 December 1977). Samples were collected in electropolished stainless steel and glass vessels and analyzed by GC-ECD, operated coulometrically. Samples were analyzed in situ as well as after storage. The northern temperate average mixing ratio was reported as 123 ppt. The latitudinal distribution is shown in Figure 3-1.

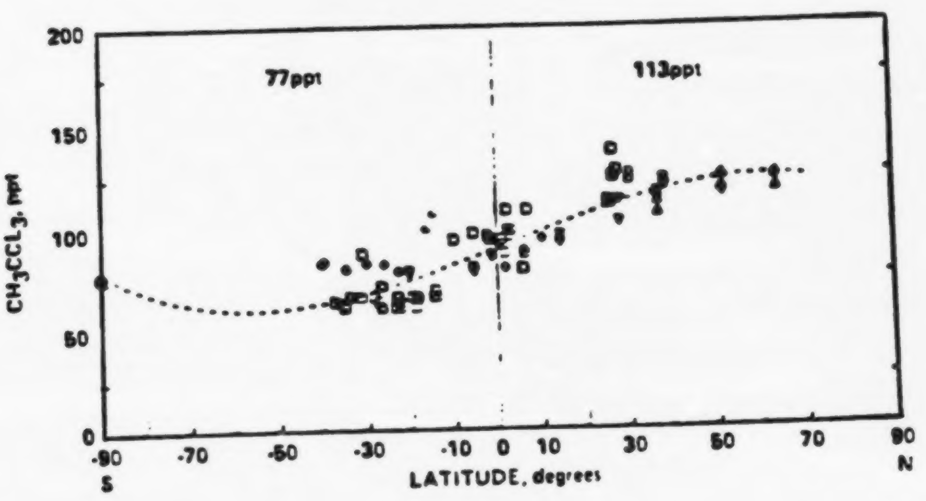


Figure 3-1. Global distribution of methyl chloroform (Singh et al., 1979a).

The vertical profile and latitudinal gradients of MC in the troposphere and lower stratosphere have been investigated by Cronn and coworkers in a series of high-altitude studies (Cronn and Robinson, 1979; Cronn et al.; 1976; 1977a; 1977b). Most recently, experiments conducted at the Panama Canal Zone (9°N latitude) and at 37°N indicated that MC tropospheric abundance was 18 percent lower at 9°N (Cronn and Robinson, 1979). Singh et al. (1979a) recorded a 17 percent difference between these latitudes (Figure 3-1). For July 1977, the average tropospheric background concentration (139 whole air samples were collected between ground level and 13.7 kilometers) was 97.3 ± 4.6 ppt at 9°N. At 37°N (Pacific Ocean west of San Francisco), an average mixing ratio of 116 ± 14 ppt was measured. Tropopause height at the Canal Zone was 15.7 kilometers. Methyl chloroform tropospheric mixing ratios did not vary significantly with increasing altitude at 9°N but there was a precipitous drop in the mixing ratio across the tropopause. This observation suggests that modeling of MC's role in stratospheric processes requires a consideration of ultraviolet photoreactivity at all altitudes.

Analysis of pressurized tropospheric samples was performed by a dual GC-ECD. The detection limit for MC was 6 ppt and the precision of analysis was ±4.2 percent. Analyses were performed on 5-ml aliquots. For the low-pressure stratospheric air samples, precision was ±7 percent with a detection limit of 2 ppt. Methyl chloroform was preconcentrated with a freezeout sample loop. Overall accuracy of analysis was estimated at about 10 percent.

In experiments conducted at 37°N (Cronn et al., 1977a), samples were collected at altitudes ranging from 6.1 to 14.3 kilometers with the tropopause height between 11 and 12 kilometers. Samples were analyzed by GC-ECD utilizing the freezeout concentration method. The average tropospheric background mixing ratio for MC in April 1977 (excluding samples within 0.8 kilometer of the tropopause) was 116 ± 14 ppt. This value is consistent with the results of Singh et al., (1979a), who obtained a value of 117 ppt at this latitude during the fourth quarter of 1977 (Figure 3-1).

When this observed mixing ratio (116 ppt) was compared with that obtained in March 1976 at 48°N (Pacific Northwest), an annual atmospheric increase in MC of 23.7 percent was calculated. Cronn et al. (1976; 1977a) collected whole air samples at altitudes ranging from 4.6 to 14.6 kilometers (average tropopause height was 10.8 kilometers) during March 1976 over Western Montana and

Idaho. The average tropospheric background mixing ratio for MC was 94.5 ± 8.2 ppt. Samples were analyzed by GC-ECD both isothermally with a 5-ml aliquot and with the freezeout concentration method. Precision of the overall method was ±4 percent.

The Washington State University (WSU) group has made several studies by aircraft of the latitudinal distribution of MC (Cronn, 1980a; Robinson, 1978; Robinson and Harsch, 1978). Interhemispheric differences of MC in the troposphere in June, 1976, were reported, with northern levels of 96 ppt and southern levels of 88 ppt (Robinson and Harsch, 1978). Lower stratospheric levels were 80 and 67 ppt, respectively. Work begun at WSU in 1976, and continuing at both WSU and the Oregon Graduate Center, has provided annual measurements of interhemispheric differences of MC of 1.67, 1.72, 1.56, 1.40, and 1.45 for 1975, 1976, 1977, 1978, and 1979, respectively (Khalil and Rasmussen, 1980; Robinson, 1978). Time-trend monitoring has been conducted nearly continuously at a ground station in eastern Washington state since July 1977 (Cronn, 1980a). Increases have exceeded 12 percent per year during that time.

Rasmussen and Khalil (1981b), from 1979 to early 1981, measured tropospheric levels of MC at six locations, ranging from 70°N to 42°S, including several measurements at the south pole (90°S). Analysis was made by EC/GC. From these measurements, a global average concentration of 115 ppt was calculated along with an annual increase of 6.7 ± 2.0 percent. This global average is consistent with the values reported by others for previous years. In contrast, however, to the rate of increase reported by Singh et al. (1979a) for the period 1975 to 1978, the rate of increase appears to be declining, which Rasmussen and Khalil (1981b) attribute to an overall reduction in the rate of emissions. The hemispheric difference in concentration reported by Rasmussen and Khalil (1981b) is consistent with that reported by Singh et al., (1979b). During the period from January 1979 to December 1980, the northern hemisphere average was 130 ppt compared to the southern hemisphere average of 99 ppt (Rasmussen and Khalil, 1981b).

Rasmussen and Khalil (1982) have obtained new estimates of the average mixing ratio of MC in both hemispheres, based on tropospheric air samples collected during the 1978 Project GAMETAG. Based on these samples, the average hemispheric levels are 117±4 ppt (Northern) and 90±3 (Southern). Data for the tropical latitudes indicate that MC levels in boundary air (0.12 to 0.36 km) are 6.4 percent higher than above it. Data limitations precluded a similar analysis for Northern latitudes.

Intermittent monitoring of MC at various urban, nonbackground and rural locations has also been conducted by Cronn and coworkers (Cronn, 1980b; Cronn and Harsch, 1979b; Cronn et al., 1979; Harsch and Cronn, 1979). Levels greater than 5 ppb have been measured in Claremont, California, with an average of 1.2 ppb during September 1978 (Cronn et al., 1979; Harsch and Cronn, 1979). Evidence of regional pollution buildup was observed in the Smoky Mountains of Tennessee in September 1978, with levels averaging 50 percent greater than background tropospheric levels typical at that time (Cronn and Harsch, 1979; Cronn et al., 1979). Values in the Caucasus Mountains of the Republic of Georgia, USSR, in July 1979, were identical to levels measured in rural eastern Washington (Cronn, 1980b).

A series of studies on the distribution and levels of MC and other halogenated hydrocarbons at various sites has been conducted by Pellizzari and coworkers (Pellizzari, 1977; 1978; Pellizzari and Bunch, 1979; Pellizzari et al., 1979). Methyl chloroform was detected in the ambient air at sites in New Jersey, New York, California, Louisiana, and Texas. Levels are included in Table 3-6. In addition, Pellizzari (1982) has detected MC as one of a number of halogenated compounds in the air near industrial and chemical waste disposal sites. The estimated levels, as measured by GC/MS, ranged from trace levels to 1.6±0.2 ppb ($8.8 \times 10^{-3} \pm 1.2 \times 10^{-3}$ mg/m^3), in the ambient air in Iberville Parish, Louisiana.

Point measurements made by Lovelock (1977b) during 1972 to 1977 resulted in a lower global average background mixing ratio (73 ppt). Air samples collected at rural sites in the British Isles indicated that, during the 5 year period, MC mixing ratios increased from 31 ppt to 97 ppt. In the southern hemisphere (Africa and Antarctica), it increased from 12 ppt to 50 ppt. Absolute accuracy of the GC-ECD method was reported as ±30 percent.

In field measurements of ambient MC levels over North America (18°N to 65°N) from October 4 to 13, 1976, Pierotti and co-workers (1980) determined an average tropospheric mixing ratio of 145 ± 25 ppt for this region. The mixing ratio dropped sharply across the tropopause and in the stratosphere, suggesting a large sink at these altitudes. These investigators suggested that the

TABLE 3-6. AMBIENT AIR MIXING RATIOS OF METHYL CHLOROFORM MEASURED AT SITES AROUND THE WORLD

Location	Type of site	Date	Maximum (ppb)	Minimum (ppb)	Average (ppb)	Reference
Alaska (70°N)		Aug. 1979 -Jan. 1981			≃ 0.155	Rasmussen and Khalil, 1981b
Antarctica						
South Pole	Remote	1/75			0.054	Robinson, 1978
South Pole	Remote	1/76			0.057	Ibid.
South Pole	Remote	1/77			0.070	Ibid.
South Pole	Remote	10/77 - 11/77			0.082	Ibid.
South Pole	Remote	1/78			0.083	Ibid.
South Pole	Remote	1/79			0.095	Khalil and Rasmussen
South Pole	Remote	Jan. 1979 - Jan. 1981	≃ 0.12	≃ 0.094		Rasmussen and Khalil, 1981b
South Pole	Remote	1/80			0.103	Ibid.
Arizona						
Phoenix	Urban	4/23-5/6, 1979	2.814	0.198	0.824 ± 0.597	Singh, et al., 1981, 1982
Arkansas						
Helena	Remote	11/30/76	≤ 1	≤ 1	≤ 1	Battelle, 1977
California						
Los Angeles	Urban	4/9-4/21, 1979	5.143	0.224	1.028 ± 0.646	Singh et al., 1981, 1982
Oakland	Urban	6/28-7/10, 1979	0.967	0.143	0.291 ± 0.161	Ibid.
San Jose	Urban	8/21-8/27, 1978	2.931	0.150	0.789 ± 0.649	Singh, et al., 1979a
Point Arena	Marine	8/30-9/5, 1978	0.158	0.115	0.132 ± 0.011	Ibid.
Claremont	Urban	9/78	5	0.3	1.2	Cronn, et al., 1979
Point Arena	Marine	5/23-5/30, 1977	0.150	0.083	0.111 ± 0.018	Ibid.
Badger Pass	High altitude	5/5-5/13, 1977	0.342	0.130	0.231 ± 0.056	Ibid.
San Francisco	Free troposphere	4/77			0.12 ± 0.01	Cronn, et al., 1977a
Riverside	Urban	4/25-5/4, 1977	3.012	0.282	0.834 ± 0.560	Ibid.

TABLE 3-6. (continued)

Location	Type of site	Date	Maximum (ppb)	Minimum (ppb)	Average (ppb)	Reference
California						
Mill Valley	Background subject to urban transport	1/11-1/27, 1977	0.895	0.107	0.313 ± 0.130	Ibid.
Yosemite	High altitude	5/12-5/18, 1976	0.126	0.073	0.104 ± 0.009	Ibid.
Palm Springs	Suburban	5/5-5/11, 1976	0.545	0.075	0.159 ± 0.075	Ibid.
Los Angeles	Urban	4/28-5/4, 1976	7.663	0.100	1.545 ± 1.538	Ibid.
Badger Pass	High altitude	May 1976	---	---	0.988 ± 0.0097	Singh, et al., 1978c
Los Reyes	Marine	12/1-12/12, 1975	0.212	0.061	0.111 ± 0.027	Singh, et al., 1979a
Stanford Hills	Background subject to urban transport	11/23-11/30, 1975	0.565	0.070	0.141 ± 0.117	Ibid.
Los Angeles Basin	Urban-suburban	4/9-4/21, 1974	2.14	0.01	0.37 ± 0.05 (24-hour)	Simmonds et al., 1974
Colorado						
Denver	Urban	6/15-6/28, 1980	2.70	0.171	0.713± 0.553	Singh, et al., 1982
Delaware						
Delaware City	Urban	7/8-7/10, 1974	0.30	0.03	0.10	Lillian et al., 1975
Hawaii						
Cape Kumakahi	Remote	Nov. 1979 - Jan. 1981			≃ 0.14	Rasmussen and Khalil, 1981b
Illinois						
Chicago	Urban	4/20-5/2, 1981	0.909	0.241	0.476 ± 0.158	Singh et al., 1982
Ireland						
Western Ireland	Remote	June/July 1974	---	---	0.048 ± 0.0172	Lovelock, 1974

TABLE 3-6. (continued)

Location	Type of site	Date	Maximum (ppb)	Minimum (ppb)	Average (ppb)	Reference
Japan						
Tokyo	Urban	9/10 - 10/27, 1975	20.60	0.20	1.70 ± 1.70	Tada et al., 1976
Tokyo		May 1974-Apr 1974	---	---	0.800	Ohta et al., 1977
Kansas						
Jetmar	Remote	6/1-6/7, 1978	0.159	0.106	0.130 ± 0.016	Singh, et al., 1979a
Louisiana						
Baton Rouge, Geismar, Plaquemine	Urban	Jan/March 1977	1.6	trace	0.11	Pellizzari et al., 1979
Maryland						
Baltimore	Urban	7/11-7/12, 1974	0.21	0.044	0.12	Singh, et al., 1979a
Missouri						
St. Louis	Urban	5/29-6/9, 1980	0.896	0.132	0.235 ± 0.135	Singh et al., 1982
New Jersey						
Seagirt	Marine	6/18-6/19, 1974	0.20	0.044	0.10	Lillian et al., 1975
Sandy Hook	Marine	7/2-7/5, 1974	0.33	0.030	0.15	Ibid.
Bayonne	Urban	March-December, 1973	14.4	0.075	1.59	Ibid.
Rahway/ Woodbridge, Boundbrook, Passaic	Urban	Sept. 1978	20.5	trace	11.4	Pellizzari et al., 1979
New York						
New York City	Urban	6/27-6/28, 1974	1.6	0.10	0.61	Lillian et al., 1975
Niagara/Falls/ Buffalo	Urban	July 1978	1.0	0.26	0.66	Pellizzari et al., 1979
Staten Island	Urban	3/26-4/5, 1981	1.43	0.22	0.468 ± 0.248	Singh et al., 1982
White Face Mountains	High altitude	9/16-9/19, 1974	0.13	0.032	0.067	Lillian et al., 1975

TABLE 3-6. (continued)

Location	Type of site	Date	Maximum (ppb)	Minimum (ppb)	Average (ppb)	Reference
Ohio Wilmington	Urban	7/16-7/26, 1974	0.35	0.030	0.097	Ibid.
Oregon Cape Meares	Remote	Jan. 1979 - Ja. 1981			≈ 0.155	Rasmussen and Khalil, 198b
Panama	Remote troposphere	July 1977			0.97 ± 0.05	Cronn and Robinson, 1979
Samoa (14°S)	Remote	Feb. 1980 - Jan. 1981			≈ 0.155	Rasmussen and Khalil, 1981b
Pennsylvania Pittsburg	Urban	4/7-4/17, 1981	1.60	0.158	0.486 ± 0.272	Singh et al., 1982
Soviet Union Caucasus Mountains	Remote	July 1979	0.12	0.15	0.13 ± 0.06	Cronn, 1980b
Tasmania Cape Grim	Remote	Oct. 1976 - March 1977 Jan. 1979 - June 1980	---	---	0.012 ± 0.003 ≈ 0.1	Fraser and Pearman, 1978 Rasmussen and Khalil, 1981b
Tennessee Smoky Mountains	Regionally polluted	September 1978	0.32	0.11	0.10 ± 0.03	Cronn and Harsch
Texas Houston, Deer Park	Urban	July 1976	5.1	trace	0.44	Pellizzari, et al., 1979

TABLE 3-6. (continued)

Location	Type of site	Date	Maximum (ppb)	Minimum (ppb)	Average (ppb)	Reference
Texas						
Pasadena Houston	Urban	5/14-5/25, 1980	1.50	0.134	0.353 ± 0.263	Singh et al., 1982
Northern Mid-Latitudes	Remote troposphere	6/76	0.11	0.07	0.095 ± 13	Robinson and Harsch, 1978
Washington						
Pullman	Remote	1/75			0.090	Robinson, 1978
Pullman	Remote	1/76			0.098	Ibid
Pullman	Remote	1/77			0.109	Ibid
Pullman	Remote	10/77 - 11/77			0.115	Ibid
Pullman	Remote	1/78			0.120	Ibid
Pullman	Remote	1/79			0.135	Khalil and Rasmussen, 1980
Pullman	Remote	1/80			0.157	Ibid
Pullman	Remote troposphere	3/76			0.095 ± 0.008	Cronn et al., 1976
Spokane	Urban	4/78			0.5	Cronn et al., 1979

data were consistent with a northern hemisphere background mixing ratio of about 100 ppt. Point measurements of MC atmospheric mixing ratios in the troposphere are shown in Table 3-6.

3.5 LEVELS FOUND IN WATER

Groundwater data available from state sources indicate that 23 percent of the 1,611 wells tested contained MC (Coniglio, 1980). Concentrations of 344 ppb were measured in discharge waters from a MC manufacturing facility (Battelle, 1977). Chow (1980) reported a level of 700 ppb in testing of residential wells near a manufacturing site. The highest level reported for drinking water is 17 ppb (Battelle, 1977). Chian and Ewing (1977) have examined surface water at various sites in the United States and found that 11 of 204 sites had MC levels greater than 6 ppb. The maximum level of MC found was 8 ppb. Bellar et al. (1974) reported that the influent level of MC to a municipal sewage treatment plant was 16.5 ppb; upon treatment, the level dropped to 9.0 ppb. Contamination of community drinking water supplies by MC and other halogenated solvents used as components of cesspool cleaners was reported (U.S.E.P.A., 1979b). It was cited that levels of MC in observation wells were as high as 5,000 ppb. The maximum level of MC found in the contaminated drinking water wells was 310 ppb. Given the high volatility of MC and the generally low levels expected in natural aquatic environments, MC is expected to be nonpersistent.

3.5 REFERENCES

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4. METABOLIC FATE AND DISPOSITION

4.1 ABSORPTION, DISTRIBUTION, AND ELIMINATION

Methyl chloroform (MC; 1,1,1-trichloroethane) is currently one of the most widely used of the chlorinated aliphatic hydrocarbon solvents. Since its introduction in the mid-1950's as a cold cleaning solvent substitute for carbon tetrachloride, MC has gained recognition as being among the least toxic of the chlorinated aliphatic hydrocarbons (Chemical Marketing Reporter, 1982) and is increasingly replacing other supposedly more toxic chlorinated solvents such as trichloroethylene (Torkelson et al., 1958; Prendergast et al., 1967; Stewart, 1968). The fact that its isomer, 1,1,2-trichloroethane, is markedly more toxic than MC (Hardie, 1964; Irish, 1963; Browning, 1965; Carlson, 1973), is in agreement with the general observation that chlorinated ethanes having chlorines on both carbon atoms are considerably more soluble in water, blood, and lipid (Table 4-1). These physical properties could be responsible in part for the manifestations of differences in chlorinated hydrocarbon toxicity (Sato and Nakajima, 1979; Clark and Tinston, 1973).

4.1.1 Oral and Dermal Absorption

While limited absorption of MC vapor through the lungs is the common route of entry into the body, MC is also rapidly and completely absorbed from the gastrointestinal tract (Stewart, 1971). Stewart and Andrews (1966) reported an instance of non-fatal acute intoxication after oral ingestion of a liquid ounce of MC (0.6 g/kg body weight,BW). The concentration of MC in the expired air was measured serially and found equivalent to an inhalation exposure of experimental subjects to 500 ppm (2,700 mg/m^3). On the other hand, MC vapor is poorly absorbed through intact skin and, unless it is trapped against the skin beneath an impermeable barrier, it is unlikely that toxic quantities can be absorbed (Stewart, 1971; Stewart and Dodd, 1964). Stewart and Dodd (1964) demonstrated, with continuous immersion for 30 min of the thumbs or hands of volunteers, that the solvent penetrates the skin, enters the blood circulation, and is excreted through the lungs in exhaled air. Fukabori and coworkers (1976, 1977) attempted a quantitation of cutaneous absorption in humans. Systemic absorption was evaluated by measurement of MC in blood and

TABLE 4-1. PARTITION COEFFICIENTS OF METHYL CHLOROFORM AND OTHER SOLVENTS AT 37°C

Compound	Vapor Press torr at 25C	Water/Air	Olive Oil/Air	Blood/Air	Olive Oil/Blood
1,1,1-Trichloroethane	125	0.93	356	3.3	108
1,1,2-Trichloroethane	25	17.1	2273	38.6	59
1,1-Dichloroethane	250	2.7	187	4.7	40
1,2-Dichloroethane	80	11.3	447	19.5	23
Trichloroethylene	436	1.3	718	9.5	76
Tetrachloroethylene	20	0.43	1917	13.1	146
Dichloromethane	400	7.6	152	9.7	16
Chloroform	250	3.5	401	10.3	39
Carbon tetrachloride	100	0.25	361	2.4	150

Adapted from Sato and Nakajima, 1979.

exhaled air and its biometabolites [trichloroethanol (TCE) and trichloroacetic acid (TCA)] in urine. After applications of the solvent to the skin of the forearm in a circumscribed area (12.5 cm^2) for 2 hours a day for 5 consecutive days, or immersion of the hands 11 times a day for 10 minute periods, the MC concentrations in exhaled air and urinary metabolites corresponded roughly to a 2-hour inhalation exposure to 10-20 ppm (54 to 108 mg/m^3) MC in ambient air. The investigators concluded that absorption through the skin for workers in direct contact with liquid MC may add to the absorption from vapor exposure.

Additional evidence that MC absorption via skin may represent a significant source of exposure is provided by the results of Jakobson et al. (1982). Application of an inhibited form of MC to the skin (3.1 cm) of anaesthetized guinea pigs resulted in peak blood levels (1.9 ug/ml) 30 minutes after exposure. Blood levels then declined to 0.66 ug/ml 6 hours after exposure MC was applied at two sites on shaved skin under an occlusive barrier. With elimination studies, using percutaneous exposure 4 hours in duration, elimination from the blood was consistent with a two-compartment model exhibiting nonlinear kinetics. During exposure, no visible skin reactions were noticed at the application sites. In comparison, Astrand (1975) obtained a level of 4 ug/ml arterial blood after a 30-minute exposure of humans to 245 ppm (1,323 mg/m^3).

4.1.2 Pulmonary Uptake and Body Burden

Several studies have been made of the pharmacokinetics of MC pulmonary uptake, distribution in the body, and metabolism after exposure to low inhalation concentrations approximating the accepted TLV-TWA concentration. Information available from these studies concerns single exposures under experimentally controlled conditions with animals or human volunteers. Little information is available regarding long-term exposure, such as may occur in the workplace or in the environment. Recent studies have greater reliability than earlier studies because of the availability of gas chromatographic methods for the analytic determination of MC and its metabolites in alveolar air, body fluids, and tissues (Schumann et al., 1982a,b; Monster et al., 1979b; Monster and Boersma, 1975; Astrand et al., 1973; Eben and Kimmerle, 1974; Briemer et al., 1974; Humbert and Fernandez, 1976, 1977; Stewart et al., 1969), although spectrophotometric methods based on adaptations of the Fujiwara reaction are still widely used by many investigators for determining urinary excretions of trichloroethanol (TCE), trichloroacetic acid (TCA), or total urine chloroderivatives of MC (Ogata et al., 1974; Imamura and Ikeda, 1973; Tanaka and Ikeda, 1968; Ikeda and Ohtsuji, 1972).

Inhaled MC rapidly equilibrates with arterial capillary blood across the lung alveolar endothelium (Astrand, et al., 1973). The rate of pulmonary uptake or absorption depends largely on the solubility of MC in blood (Ostwald solubility coefficient) and hence the blood/air partition coefficient (Table 4-1). Vapors with a high partition coefficient are absorbed into the body readily and may exhibit selective partitioning into various tissues. Conversely, vapors with a low partition coefficient are expected to approach steady-state tissue levels slowly. This is likely since partition occurs more rapidly with venous blood and alveolar air, and thus vapors are more rapidly eliminated into expired air following exposure. In comparison with other common solvents in Table 4-1, MC possesses a relatively low blood/air partition coefficient of about 3.3 at 37°C.

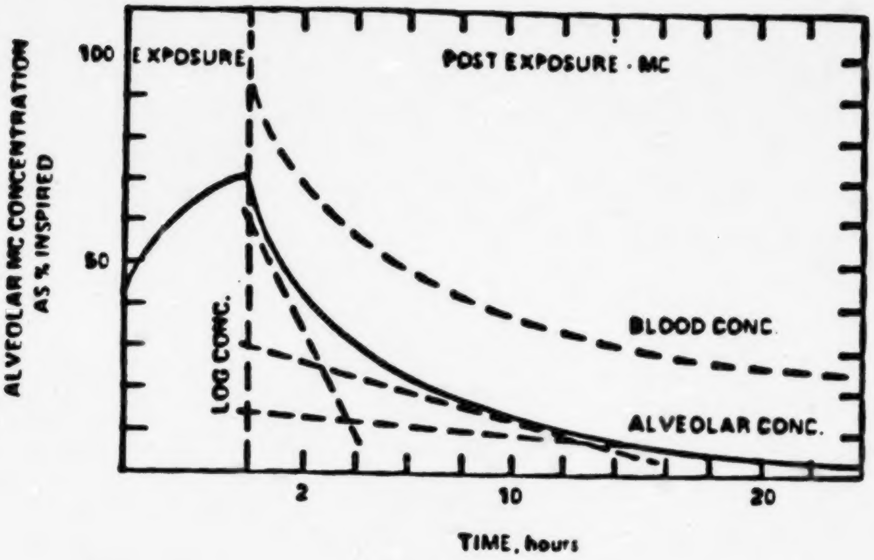

Figure 4-1. Absorption and pulmonary elimination of MC, and blood concentration (see text for explanation).

Davidson, I.W.F., 1980.

The magnitude of MC uptake (dose, burden) into the body is directly related to the following factors: 1) concentration of MC in the inspired air; 2) duration of exposure until steady-state is reached; 3) pulmonary ventilation during exposure; 4) blood/ air partition coefficient; 5) rates of diffusion into, and solubility in, the body tissues; 6) total body-lipid repository, and 7) metabolic rate. Consequently, during exposure at a given inspired air concentration, pulmonary uptake and retention is initially large and gradually decreases to a minimum steady-state value as total body equilibrium (and body burden) with inspired air concentration is reached. At this steady-state condition, pulmonary uptake balances the pulmonary and other routes of elimination, including metabolism. For any given breath cycle during exposure, the proportion of MC absorbed and retained by the body is equal to the inspired air concentration (C_I) minus the end alveolar air concentration (C_A) and, since pulmonary uptake is a function of inspired air concentration, the percent retention is:

$$\%\text{ retention of inspired air concentration} = \frac{C_I - C_A}{C_I} \times 100 \qquad (1)$$

This value is large at the beginning of exposure, but gradually decreases as total body equilibrium is approached (Figure 4-1). The percent retention value is independent of the inspired air concentration. During experimental exposures of subjects to 70 and 140 ppm (378 and 756 mg/m^3) MC for 4 and 8 hours, both Monster et al. (1979b) and Humbert and Fernandez (1977) found retention to be 30 percent of inspired air concentration at an equilibrium reached after 4 hours of exposure.

The total amount (dose, Q) of MC retained in the body during an inhalation exposure can be estimated by multiplying percent retention by the volume of air inspired during the exposure period, or:

$$Q = (C_I - C_A)\ \dot{V} \cdot T \qquad (2)$$

where $\dot{V}$ is ventilation rate (ℓ/min) and T is exposure period (min). Since the retention value decreases exponentially during the exposure until equilibrium is reached (Figure 4-1), either experimental measurements of retention at frequent intervals during exposure (Monster et al., 1979b) or integration over the experimentally determined retention function is required (Humbert and Fernandez, 1977). The exponential nature of the retention curve is due to first-order kinetics of saturation of body compartments with MC.

Table 4-2 shows the amounts of MC absorbed into the body during inhalation exposures for volunteers from the studies of Monster et al. (1979b) and Humbert and Fernandez (1977). Monster and his coworkers estimated pulmonary uptake of MC by multiplying the minute volume by percent retention during single 4-hr exposures to 70 ppm and 145 ppm (378 and 783 mg/m^3). They observed a direct proportionality between uptake and inspired air concentrations of MC. Similar results were obtained by Humbert and Fernandez for volunteers exposed for 8 hours to 72 ppm and 213 ppm (389 and 1,150 mg/m^3). Comparison of pulmonary uptake for 4-hr and 8-hr (Table 4-2) exposures indicates that the amount of MC retained is also proportional to duration of exposure until a steady-state is reached, although the values for uptake determined by Humbert and Fernandez are 40 percent lower than those of Monster et al. This variation can be ascribed to differences in the experimental methodologies and average minute volume. Nonetheless, these experimental results indicate that the body burden resulting from an 8-hr inhalation exposure to 350 ppm (1,890 mg/m^3) (TLV-TWA) approximates 1.5 to 2 g of MC for a normal 70-kg man.

TABLE 4-2. ESTIMATED UPTAKE OF MC DURING A SINGLE 4-HR INHALATION EXPOSURE (AVERAGE BODY WEIGHT, 77 kg; 67 kg LEAN BODY MASS), MONSTER ET AL., 1979

Subject	Exposure Concentration		
	70 ppm (at rest*) Uptake, mg	145 ppm	142 ppm*, with work (100 watt) Uptake, mg
A	140	305	435
B	240	520	610
C	200	465	540
D	185	395	560
E	200	425	575
F	190	465	505
Av.	193	429	538

*Ventilation minute volume increased from average of 10.7 ℓ/min. at rest to 30.6 ℓ/min during light work.

ESTIMATED UPTAKE OF MC DURING A SINGLE 8-HR INHALATION EXPOSURE (AVERAGE BODY WEIGHT 74 kg), HUMBERT AND FERNANDEZ, 1977

Subject	Exposure Concentration*	
	72 ppm	213 ppm
	Uptake, mg	
BH	293	921
JC	274	912
JO	277	--
Av.	281	917

*Average ventilation minute volume 5.7 ℓ/min.

The body uptake of MC increases with the duration of inhalation exposure and with physical work or exercise. Monster et al. (1979b) found that during a 4-hr exposure to 142 ppm (767 mg/m^3) MC, with physical activity equivalent to light physical work (100 watts), pulmonary uptake increased from 429 mg to 538 mg MC, an increase of 25 percent (Table 4-2). This increase was primarily due to an increase of ventilation from 10.7 ℓmin^{-1} sedentary to 30.6 ℓmin^{-1} with work. While it might be expected from equation (2) that the increased uptake should be directly proportional to the ventilation rate increment, an increase in ventilation also tends to increase alveolar elimination of MC from pulmonary venous blood. Similar observations were made by Astrand et al. (1973) with volunteers exposed to an MC inhalation concentration of 250 and 350 ppm (1,350 and 1,890 mg/m^3) for 30 minutes at rest, alternating with identical exposure plus 50 watts of light work. Table 4-3 shows that their subjects responded to this work with a 3-fold increase of pulmonary ventilation, nearly a 2-fold increase in cardiac output, and a 50 percent increase in arterial blood concentration, which is an index of pulmonary uptake. Also, end alveolar concentration of MC increased while retention decreased from 50 to 33 percent with work. Therefore, physical activity during MC exposure increases the uptake and body burden, but the increase is not directly proportional to increased ventilation and is self-limited by a compensatory increase of pulmonary elimination. For solvents like MC, with a low blood/air partition coefficient, physical activity has a smaller effect on net pulmonary uptake and body retention than those solvents with a higher blood/air partition coefficient (e.g., trichloroethylene, perchloroethylene, dichloromethane; Table 4-1; Monster, 1979).

During inhalation of MC, and in the elimination phase after exposure, the concentration in arterial blood leaving the lung always is directly proportional to the alveolar concentration (Monster et al., 1979b; Humbert and Fernandez, 1977; Astrand et al., 1973; Gamberale and Hultengren, 1973; Eben and Kimmerle, 1974). Since at equilibrium the end alveolar air concentration is proportional to inspired air concentration, blood concentration of MC is also related to inspired air concentration (Monster et al., 1979b; Humbert and Fernandez, 1977; Astrand et al., 1973). This fixed relationship between alveolar air and blood concentration is defined by the blood/air partition coefficient for MC. Figure 4-2 illustrates this linear relationship for a

TABLE 4-3. MEAN VALUES AND SEM FOR 12 MALE SUBJECTS AT REST AND EXERCISE FOR 30 MINUTE PERIODS

MC	Ventilation BTPS ℓ/min	Cardiac output ℓ/min	Alveolar conc ppm	Blood arterial conc. μg/g
At rest				
250 ppm	6.6 ± 0.4	5.1 ± 0.4	125 ± 6	3.0 ± 0.2
350 ppm	6.6 ± 0.4		179 ± 13	5.0 ± 0.5
50 Watt				
250 ppm	22.5 ± 1.0	9.7 ± 0.6	168 ± 7	4.5 ± 0.2
350 ppm	21.8 ± 1.1		239 ± 17	7.2 ± 0.4

From Astrand et al. (1973).

volunteer exposed for 30 minutes to increasing increments of MC concentration in inhaled air. The relationship was independent of the duration of exposure over the time period studied. Eben and Kimmerle (1974) exposed rats to 204 ppm (1,101 mg/m^3) for 8 hours daily, 5 days a week for 14 weeks and found that the blood concentration of MC determined immediately after daily exposure remained constant during the entire 3 month period, suggesting that steady-state was attained.

The blood/air partition coefficient, as determined from in vivo measurements of alveolar air concentration and blood concentration of MC, agrees well with the in vitro value of 3.3 at 37°c determined by Sato and Nakajima (1979) (Table 4-1). Table 4-3 summarizes the data of Astrand et al. (1973), determined for sedentary men exposed to 250 and 350 ppm (1,350 and 1,890 mg/m^3) MC for 30-min periods alternating with 30-min periods of physical activity. The ratios of arterial blood concentration (μg/g) to alveolar MC concentration remain nearly constant over a 2-fold range of alveolar concentrations, with an average value of 5. Monster et al. (1979b) estimated from their study of men exposed to 70 and 142 ppm (378 and 767 mg/m^3) MC a blood/alveolar air concentration ratio of 6. In comparison to other solvents (Table 4-1), MC has a relatively small blood/ air partition coefficient and, hence, for equivalent ambient air exposure concentrations the blood concentration of MC is proportionally lower than for other solvents.

The amount of MC pulmonary uptake is influenced by total body weight and also by the total fat content of the body (average body fat = 8 percent of

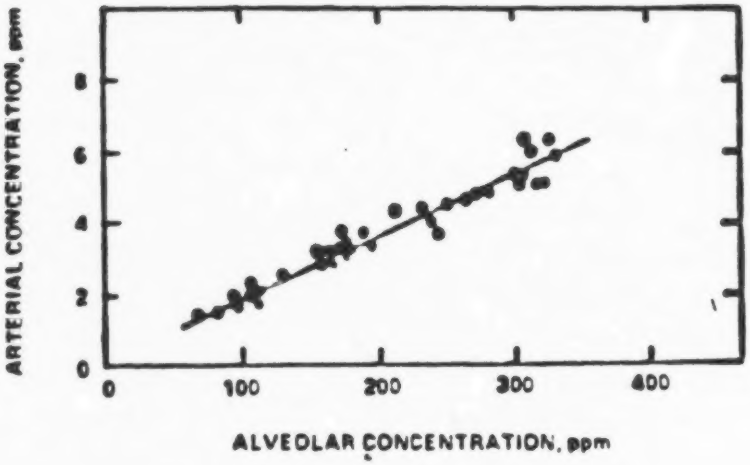

Figure 4-2. Relationship between methyl chloroform concentration in alveolar air and arterial blood. Data from one subject. Product moment correlation: r = 0.985. Data from one subject exposed to 30-min. periods of MC. Alveolar air samples and arterial blood samples.

From Gamberale and Hultengren, 1973.

body weight). The capacity of adipose tissue to absorb MC in vivo is determined by the product of adipose tissue volume and the lipid solubility of MC. The olive oil/blood partition coefficient for MC (108 at 37°C) is higher than for most other structurally related solvents (Table 4-1) and, therefore, the capacity of adipose tissue for MC is relatively high. However, because of the low rate of perfusion (5 percent of cardiac output), the time needed to saturate adipose tissue is large in comparison with that for other tissues. Also, since the blood/air partition coefficient for MC is lower than that of other solvents, the amount of MC in adipose tissue (concentration) at the end of an exposure of similar duration will be relatively lower. Monster (1979) suggests that because of the high solubility of MC in adipose tissue, tissue storage of MC under non-steady state conditions will vary with repeated daily exposures, particularly in obese persons. This concept is supported by the observations of Savolainen, Vainio and coworkers (1977, 1978), who exposed rats to MC (500 ppm; 2,700 mg/m^3) 6 hr daily for 5 days and determined MC concentrations in perirenal adipose tissue and in other body tissues. Their data, shown in Table 4-4, indicate that measureable amounts of MC remained in perirenal fat tissue 18 hours after the previous exposure of day 4, and markedly increased further with a 6-hr exposure on day 5. The adipose tissue/blood partition coefficient calculated from these data was 21, as compared to 1.6 for brain and liver tissues. On the other hand, Eben and Kimmerle (1974) exposed rats for 14 weeks (8 hr daily, 5 day per wk) to 204 ppm (1,101 mg/m^3) MC but failed to find MC in adipose or other tissues and concluded that MC did not accumulate with chronic exposure. However, the average exposure concentration for their rats was lower than that used by Savolainen et al. (500 ppm vs 204 ppm; 2,700 vs 1,101 mg/m^3). It should be noted that low-level, prolonged exposures would be expected to result in steady-state tissue concentrations. Under these conditions no further MC would be expected to partition into lipid-rich tissues.

4.1.3 Tissue Distribution

During exposure to MC, distribution of the compound throughout the body and the amount concentrated by each tissue is primarily governed by the blood concentration, the blood perfusion rate, and the affinity of MC for respective tissues, as determined by individual tissue/ blood partition coefficients. In comparison with other chlorinated hydrocarbon solvents that are known to be distributed widely in the body, MC has one of the highest lipid/ blood partition coefficients (108 at 37°C, Table 4-1) and would distribute into all body tissues, particularly those high in lipid content, such as brain and adipose tissue (Holmberg et al., 1977). Table 4-4 shows the concentrations of MC in liver, brain, and adipose tissue of rats exposed to 500 ppm (2,700 mg/m^3) in their inspired air for 6 hours daily for 5 days (Savolainen et al., 1977). Adipose tissue appears to have a partition coefficient with blood of approximately 20, and brain tissue levels are also greater than blood concentration. In man, MC readily passes the blood-brain barrier, as evidenced by the concentrations in the brain reported by Caplan et al., (1976) and in the cerebrospinal fluid (Larsby et al., 1978). While it has not been demonstrated directly to cross the placental barrier into the fetus, it may be expected to do so (Laseter and Dowty, 1977) like other highly lipid-soluble haloalkanes. Trichloroethanol (TCE), a major metabolite of MC, is known to cross readily into the fetus (Bernstine, 1954, 1957). Leighty and Fentiman, Jr. (1981) have recently provided in vitro evidence that TCE, upon incubation in a rat liver microsomal system fortified with coenzyme A, appears to conjugate with palmitic acid. While there is no report of MC occurring in colostrum or milk of nursing mothers, it may be expected to distribute readily into these compartments because of their high lipid content.

4.1.4 Pulmonary Elimination

Figure 4-1 shows schematically the time-course of pulmonary elimination of MC after exposure. At termination of exposure, MC immediately begins to be eliminated from the body into the lungs with blood concentration and alveolar air concentration describing parallel exponential decay curves with three major components. These components represent first-order passive diffusions of MC from three major body compartments: (1) most rapidly from a vessel-rich group of tissues (VRG) with high blood flow and high diffusion rate constant (VRG: brain, heart, kidneys, liver, endocrine, and digestive system), (2) more slowly from the lean body mass (MG; muscle and skin) and (3) from adipose tissue (FG) (Fiserova-Bergerova and Holaday, 1979). The rate constants for the passive diffusion from VRG, MG and FG compartments are dependent on both the arterial blood flow/tissue mass and the relative solubilities of MC in the tissues of these compartments (tissue/ blood partition coefficients). However, the ranking of half-times ($t_{1/2}$) of elimination of MC is VRG < MG < <FG

TABLE 4-4. TISSUE CONTENT (RAT) OF METHYL CHLOROFORM (MC) AFTER CHRONIC INHALATION EXPOSURE OF 500 ppm*

Exposure on 5th day hr.	Cerebrum	Cerebellum	Liver	Perirenal fat	Blood
		nmolMC/g wet weight ± range			
0	0.15 ± 0.03	0.17 ± 0.03	0.15 + 0.01	16.9 + 0.5	0.08 ± 0.01
2	14.6 ± 1.1	14.0 ± 2.2	14.7 ± 0.04	183.5 ± 10.7	11.5 ± 2.0
3	13.4 ± 0.60	13.2 ± 0.8	15.7 ± 3.3	218.9 ± 63.4	8.5 ± 1.0
4	12.2 ± 0.40	15.9 ± 1.5	16.2 ± 2.8	261.2 ± 19.1	12.7 ± 2.9
6	15.6 ± 4.6	21.3 ± 9.6	21.3 ± 0.4	276.0 ± 30.1	13.1 ± 1.9

*Measurements were performed on the 5th day of exposure after 4 previous daily exposures, 6 hr daily.

From Savolainen et al. (1977).

and is independent of the body burden. The areas under the alveolar or blood elimination curves in Figure 4-1 are proportional to the quantity of MC absorbed during exposure. The body burden can be obtained by integrating the exponential functions from the time immediately at the end of exposure to infinity.

The precise half-times of elimination of MC from the three major body compartments have not been well established. Monster et al. (1979b), who exposed subjects to 70 ppm and 145 ppm (378 and 783 mg/m^3) for 4 hr, estimated from decay curves of MC in blood and exhaled air half-times of elimination of 9.2 and 26 hours for the MG and FG compartments, respectively. Humbert and Fernandez (1977) determined the exponential decay of alveolar air concentration after 8 hours exposure of subjects to 72 and 213 ppm (389 and 1,150 mg/m^3) MC. These investigators calculated half-times of elimination for compartments VRG, MG, and FG as 0.8 hours, 7 hours, and 35 hours, respectively. From the post-exposure alveolar concentration curves published by Stewart and his associates (Stewart and Andrews, 1966; Stewart et al., 1969; Stewart, 1971) for subjects singly and repeatedly exposed to various inhalation concentrations of MC, the half-time of elimination for MG and FG can be estimated as approximately 14 and 24 hours, respectively. The long half-time of elimination (24 to 35 hours) from the adipose tissue compartment observed by these investigators reflects the high lipid/blood partition coefficient of MC and indicates that complete elimination of MC from this compartment requires at least 4 to 5 days. Experimentally, both Monster et al. (1979b) and Humbert and Fernandez (1977) observed that, after single controlled inhalation exposures, pulmonary elimination was not complete for 6 to 10 days as determined by the continued presence of MC in alveolar air. The possibility of significant partitioning into tissues upon repeated daily exposures to this solvent (Laseter and Dowty, 1977), however, is offset in part by the low blood/air partition coefficient (Table 4-1) which, for a given exposure concentration, limits pulmonary absorption and body dose.

4.1.5 Elimination by Other Routes

There is no report in the literature of significant elimination of MC by any route other than pulmonary. MC is poorly soluble in water, even when compared with other chlorinated hydrocarbons (Table 4-1), and with its high lipid/water partition coefficient, MC is unlikely to be excreted unchanged in the urine in any significant amounts. Studies of chlorinated compounds in the urine after exposure of animals and humans to MC have not demonstrated its appearance in urine (Schumann et al., 1982a; Monster et al., 1979; Eben and Kimmerle, 1974; Humbert and Fernandez, 1977; Seki et al., 1975; Stewart et al., 1961; Hake et al., 1960). Since highly lipid soluble substances like MC readily cross into the intestinal lumen, some fecal and flatus excretion can be expected from inhalation exposures. After controlled inhalation exposures, Humbert and Fernandez (1977) were able to account for 88 to 100 percent of an estimated retained dose as unchanged MC in postexposure exhaled air and as metabolites of MC in urine. However, Monster et al. (1979b) could account for only 60 to 80 percent; furthermore, they noted that the percentage recovered decreased with higher exposure doses.

4.2 BIOTRANSFORMATION

MC has long been known to be metabolized to only a very limited extent by mammals. The generally accepted metabolites of MC -- trichloroethanol (TCE), TCE-glucuronide, and trichloroacetic acid (TCA) -- are excreted primarily by the kidney, but very small amounts of TCE (<1 percent) are excreted by the lungs (Monster et al., 1979b). TCE-glucuronide is also excreted to an unknown extent in bile (Owens and Marshall, 1955).

Filser et al. (1982) evaluated a variety of compounds, including MC, for their ability to stimulate the endogenous production of acetone. This study was based on previous observations that certain haloethylenes caused acetonemia in rats (Filser and Bolt, 1980). Exposure of rats (Filser et al., 1982) to 1,000 ppm (5,400 mg/m^3) MC for up to 50 hours did not stimulate acetone production as measured by gas chromatographic analysis of exhaled air. Furthermore, these investigators reported that the metabolic rate of MC was below their limit of detection. Data supporting this latter observation were not provided.

4.2.1 Magnitude of MC Metabolism

More than 20 years ago, Hake and his coworkers (1960), using ^{14}C-labeled MC, determined that less than 3 percent of MC is metabolized by rats. More recently, estimates of the extent of metabolism in man have been made from controlled inhalation exposures with unlabeled MC (Seki et al., 1975; Monster et al., 1979b; Humbert and Fernandez, 1977). From the experimentally determined retained dose and the amounts of MC metabolites excreted into the urine, the percent of the dose metabolized in man is estimated to be about 6 percent.

Hake et al. (1960) found that 98.7 percent of a dose of MC given to rats was eliminated unchanged via the lungs. These investigators injected 1,1,1-trichloroethane-1-^{14}C (700 mg/kg) intraperitoneally into 3 rats (170-183 g), which were then placed individually in a Roth metabolism unit with air traps for ^{14}C-MC (cold toluene), $^{14}CO_2$ (NaOH solution) and finally a trap for "metabolites" (quartz-tube furnace and halogen absorber that converted any halogenated hydrocarbon to inorganic halogen and CO_2, and absorbed the halogen). Each rat was kept in the unit for 25 hours, during which time urine and feces were collected. At necropsy at 25 hours, blood and tissue samples were analyzed

TABLE 4-5. HAKE ET AL. (1960) RECOVERY EXPERIMENT WITH RATS (3) INTRAPERITONEALLY INJECTED WITH ^{14}C-MC (700 mg/kg)

	Average % dose
Expired Air	
Unchanged MC (by isotopic dilution)	97.6
Unknown compound detected by furnace (assumed to be unchanged MC)	1.1
$^{14}CO_2$ (in NaOH) 70% within 4 hr; 100% within 12 hr	0.5
Urine	
TCE-glucuronide + other volatile compounds but no detectable TCA	0.85
Feces	
Uncharacterized	0.03
Tissues	
Uncharacterized except skin (90% unchanged MC)	0.18

for total ^{14}C-activity. The ^{14}C-MC used in the experiments was synthesized by the investigators and was determined by paper chromatography to be 99 percent pure, with possible contamination by 0.4 percent 1,1,2-trichloroethane and 0.5 percent 1,1-dichloroethane. Their findings, summarized in Table 4-5, indicate that metabolism of MC in the rat is limited to about 2 percent of a very large dose. However, only TCE-glucuronide was identified as a metabolite in the urine, and the source of the $^{14}CO_2$ in expired air could not be defined because of the presence of small amounts of ^{14}C-1,1,2-isomer and ^{14}C-dichloroethane in the dose.

Recently, Schumann and coworkers (1982a) evaluated pharmacokinetic parameters of ^{14}C-labelled MC to characterize the disposition of the inhaled compound in male Fischer 344 rats and B6C3F1 mice. The animals, ranging in age from 2.5 to 3.5 months, were exposed to 150±9 or 1,500±90 ppm [C^{14}] MC (810 or 8,100 mg/m^3) for 6 hours and elimination of C^{14} activity was followed for 72 hours. As other investigators have found, Schumann and coworkers also observed that body burden, end-exposure blood levels, and tissue concentrations of MC were found to increase in direct proportion with exposure concentration. It was also observed that, as others have found, that MC was more concentrated in the lipid stores of both species than in the liver or kidneys immediately following exposure. However, only 2 percent or less of the initial radioactivity remained 24 hours after exposure ceased. Thus, it is reasonable to conclude that MC has little potential for bioaccumulation in these species.

Schumann et al. observed that between 94 and 98 percent of the total recovered radioactivity in rats and between 87 and 97 percent of that in mice was unchanged MC in expired air. These data are in general agreement with the observations of others reported in this section. The remaining radioactivty consisted of either $^{14}CO_2$ or nonvolatile radioactivity in urine, feces, and carcass.

Of particular interest is the observation by Schumann and coworkers that biotransformation of MC appears to be a saturable and dose-dependent process in both species. Over the 10-fold exposure range, a 2 to 3-fold increase in the mean micromole-equivalent of MC metabolized per kilogram of body weight was observed in both species. Species differences noted were (1) a greater rate of pulmonary clearance of MC in mice relative to rats, (2) end-exposure blood levels, (3) and log-linear elimination constants for two-compartment (rats) and three-compartment (mice) linear models. As the authors concluded, these differences can reasonably be ascribed to species differences in respiratory minute volume and metabolism. Coupled with the observations of Eben and Kimmerle (1974) the results of Schumann and coworkers suggest that saturation of metabolic pathways occurs somewhere in the range of 500 to 1,500 ppm (2,700 and 8,100 mg/m^3) in these rodent species.

The pharmacokinetic description and biochemical basis of saturable metabolism in relation to a variety of organic compounds is comprehensively discussed in a series of reports by Anderson and coworkers (1980) and Anderson (1981a, b, c).

In a companion study, Schumann and coworkers (1982b) determined that the fate of inhaled MC is not altered upon repeated exposure of male Fischer 344 rats and B6C3F1 mice. Both rats and mice were exposed to 1,500 ppm (8,100 mg/m^3) unlabeled MC for 16 months and, on the last exposure, to ^{14}C-MC. The fate of ^{14}C-MC was followed for 72 hours and compared to age-matched controls exposed concurrently to chamber air for 16 months prior to receiving the single ^{14}C-MC exposure. Results showed that prior repeated exposure did not significantly alter the quantity of MC excreted via the pulmonary route compared to those singly exposed, of either species. Although the mean end-exposure body burden of ^{14}C-activity was about 2-fold greater in mice than rats, it did not differ significantly between the singly and repeated exposed groups of rats or mice. Per kg body weight, mice were observed to metabolize about 5-fold more MC than did rats. Immediately after the end of the final 6-hour exposure, ^{14}C-activity was found in the liver, kidney, and adipose tissue. After 72 hours postexposure, levels in all three sites decreased appreciably; activity was not detectable in adipose tissue of mice nor in liver of rats. Prior repeated exposure to MC did not significantly alter the concentration of ^{14}C-activity in any tissue of either species.

When data obtained in the study were compared to similar data obtained during the course of exposure to younger rodents (Schumann et al., 1982a), an apparent age-related difference in metabolism was noted. The apparent effect was greater in mice; there was a 2-3 fold increase in body burden and a 5-6 fold greater extent of metabolism of MC in the 18-month-old mice compared to the 2.5 to 3.5-month-old mice that had been exposed to 1,500 ppm (8,100 mg/m^3) ^{14}C-MC in only a single 6-hour period. One factor that could account for the increased body burden and metabolism is a slower rate of pulmonary clearance in the older animals. The older rats cleared about 50 percent less ^{14}C-MC during the first three hours after exposure relative to younger rats (Schumann et al., 1982a); the difference was not as great in mice.

Man also appears to possess a very limited capacity for metabolism of MC. Table 4-6 summarizes data taken from several investigative studies showing the amount of urinary metabolites excreted after exposure to various concentrations (4.3 to 213 ppm; 23.2 to 1,150 mg/m^3) of MC in inspired air. Seki et al. (1975) surveyed workers in 4 printing plants where MC was the sole organic solvent in use. The workers were exposed 8 hours daily, 5 1/2 days per week, over a period of at least 5 years. Urine samples were collected in the latter half of the work week. Their data in Table 4-6 show a proportional increase of both TCE (as glucuronide) and TCA, and also total trichlorinated compounds (TTC) with increased air concentrations of MC. Seki et al. expressed their data as a linear relationship between inspired MC concentration and urinary metabolite excretion, with an added constant increment presumably due to continued excretion from the previous day's exposure. From this observation and from evidence of continued excretion during exposure-free weekends, they suggested that MC accumulates in the body up to a steady-state body burden defined by the air concentration of each daily exposure. Seki et al. also noted that the amounts of metabolites excreted daily in the urine of these workers were less than 5 percent of that observed with comparable exposures to trichloroethylene, a compound that Monster (1979) has shown to be metabolized from 60 to 80 percent to TCE and TCA. This comparison suggests that about 5 percent or less MC is metabolized.

The data (Table 4-6) of Monster et al. (1979b) and of Humbert and Fernandez (1977) were obtained from subjects given single 4-hr and 8-hr exposures to 70 and 145 ppm (378 and 783 mg/m^3), and 72 and 213 ppm (389 and 1,150 mg/m^3) MC, respectively. Total urinary excretion of TCE (glucuronide) and TCA is observed to be proportional to the inspired air concentration of MC and to the expected body burden from these exposures (with duration of exposure also taken into account). Both these research groups attempted a balance study by estimating the retained body dose of MC either by measuring lung clearance during exposure (Monster et al., 1979b), or by integrating over the MC alveolar air decay curve to infinite time postexposure (Humbert and Fernandez, 1977). The percentages of the retained dose metabolized to TCE and TCA were 2.5 and 6.3 percent, respectively. The difference can be ascribed to the different methodologies used for estimating body dose and their inherent imprecisions. In both studies, the percentages of MC metabolized were found to be independent of the retained dose (Table 4-6). A similar observation with rats was made by Eben and Kimmerle (1974), who measured urinary excretion of TCE and TCA for 3 days after a 4-hr inhalation of MC at 221 and 443 ppm (1,193 and 2,392 mg/m^3). The amounts of the metabolites excreted were proportional to the inspired concentration of MC. A 1.7-fold increase in the quantity of urinary metabolites was measured with the 2-fold range of exposure levels. In rats, the urinary ratio of TCE/TCA was 20/1 rather than the 3/1 observed in humans (Table 4-6).

Caperos et al., (1982) have developed a kinetic model simulating occupational exposures and one which may be suitable for biologic monitering. This model was reported to be consistent with the experimental data of Humbert and Fernandez (1977). The results of the simulation of varying workday exposures suggested that TCE is the most sensitive and representative indicator of exposure; fluctuatuions in exposure concentration had a marked influence upon urinary TCE concentrations, but no effect upon urinary TCA.

A controlled human exposure study designed to determine if simultaneous measurement of MC and Pco_2 in alveolar air represents a useful technique by which MC exposures can be monitored was conducted by Guillemin and Gubéran (1982). A linear relationship between MC levels and Pco_2 in alveolar air samples was demonstrated. Both MC and Pco_2 levels varied, depending on the technique used to collect alveolar air samples and the extent to which the eight volunteers hyper- or hypoventilated. Analysis of variance for those tests that used a "standard" sampling technique showed an average coefficient of variation of 5.6 percent. During this series, the sample was collected during the last part of a prolonged (but not forced) expiration following a normal inspiration. All 8 volunteers were exposed, at rest, 4 hours both in the morning and afternoon to MC ranging in concentration from 203 to 236 ppm (1,096 to 1,274 mg/m^3). Alveolar sampling was performed on the first postexposure day between 8 and 12 a.m. The results demonstrated that MC and Pco_2 should be corrected for hyper- and hypoventilation and for dilution of alveolar air with dead space air by a proportional adjustment of MC concentration at the mean

TABLE 4-6. RELATION BETWEEN INHALATION EXPOSURE AND URINARY METABOLITES OF MC

Seki et al., 1975

Average concentration of metabolites in urine samples from workers daily exposed to MC.

Plant	Air conc. MC, ppm	No. Subjects	TCE*	TCA	TTC/g creatinine
			mg/ℓ		
A	0	30	0	0	0
B	4.3	10	1.2	0.6	2.1
C	24.6	26	5.5	2.4	6.8
D	53.4	10	9.9	3.6	15.0

Monster et al., 1979b

Averaged amounts of metabolites in total urine collected 70-hr post single exposure (4 hr).

Air Conc. MC, ppm	No. Subjects	TCE* mg	TCA mg
72	6	5.5	1.5
145	6	11.5	2.8
Estimated as % retained dose		2%	0.5%

Humbert and Fernandez, 1977

Averaged amounts of metabolites in total urine collected for 12 days post single exposure (8 hr).

Air cond. MC, ppm	No. Subjects	TCE* mg	TCA mg
72	3	15.2	5.2
213	2	30.7	13.0
Estimated as % retained dose		4.6%	1.7%

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*TCE found as glucuronide.

normal alveolar Pco_2 or by disregarding the samples with a Pco_2 outside the normal range.

A reasonable conclusion from these studies is that MC is minimally metabolized by man on the order of 3 to 6 percent of the inhaled dose. The percentage of the dose metabolized is constant and independent of the body dose (at least up to 213 ppm; 1,150 mg/m^3), which suggests that some factor other than the capacity of the metabolizing system is the limiting one (e.g., hepatic extraction).

4.2.2 Kinetics of Blood and Urine Metabolites

The blood and urinary metabolites of MC (total amount, excretion ratios, and excretion time-course) are of interest as quantitative indices of exposure and body burden. However, the known metabolites of MC--TCE, TCE-glucuronide, and TCA -- are not pathognomonic of MC, but are also metabolites of other chlorinated hydrocarbons, e.g., trichloroethylene.

From studies of men exposed to 70 and 145 ppm (378 and 783 mg/m^3) MC inhaled for 4 hours, Monster et al. (1979b) found that the TCE concentration in blood was proportional to both the inspired concentration and the blood concentration of MC. TCE blood concentration was about 4 percent that of MC [0.2 mg ℓ^{-1} and 0.09 mg ℓ^{-1} TCE for 145 and 70 ppm (783 and 378 mg/m^3) MC inspired, respectively]. After termination of exposure, blood TCE concentration declined exponentially with a half-life of 10 to 12 hours. Urinary appearance of TCE and TCE-glucuronide paralleled the disappearance of blood TCE, and daily excretion decreased with a half-time of renal elimination of 10 to 12 hours. This value is in agreement with that observed after ingestion of TCE itself (Briemer et al., 1974; Muller et al., 1974). In contrast to the first-order blood decay kinetics of TCE, blood concentrations of TCA progressively increased after the end of MC exposure for about 40 hours before declining exponentially with a half-life of 70 to 85 hours. Consequently, TCA appeared in the urine in almost equal daily amounts for 3 days before decreasing. Exogenous TCA administered to men has a similarly long half-time of renal elimination of 50 to 82 hours, presumably because of very tight non-covalent binding to plasma proteins (Paykoc and Powell, 1945; Muller et al., 1974). Therefore, the rise in plasma concentration of TCA during the 24 to 48 hours period following exposure is due to a rate of formation of TCA from TCE greater than the rate of renal elimination of TCA. Similar observations on daily urinary excretion of TCE, TCE-glucuronide, and TCA following acute MC inhalation exposure have been made in man by Humbert and Fernandez (1977), and in rats by Eben and Kimmerle (1974).

Stewart et al. (1969) investigated urinary metabolite excretion in men repeatedly exposed to MC (500 ppm; 2,700 mg/m^3), 7 hours per day for 5 days). The daily ratio TCE/TCA during exposure remained relatively constant (about 2.8), but rapidly decreased within several days after exposure (5th day, 0.4), indicating that the daily urinary TCE excretion decreased while the TCA excretion decreased at a lesser rate or may have gradually increased. Eben and Kimmerle (1974) also chronically exposed rats for 14 weeks (8 hours daily, 5 days per week) and measured blood levels of MC, TCE, and TCA, as well as daily urinary excretion. Blood concentrations of MC and TCE (determined immediately after daily exposure) remained essentially constant during the entire 14 week period, with a concentration ratio of MC:TCE of 10:1. Weekly urinary excretion of TCE reached a plateau within 3 to 4 wk, whereas TCA weekly excretion was constant throughout the entire 14-wk period. The urinary excretion ratio TCE/TCA was thus initially low, but after 3 to 4 weeks exposure reached a constant value of approximately 18.

These findings show that the daily urinary ratio of TCE/TCA (mg/day) during chronic MC exposure of both man and rats is determined by the relative rates of metabolic formation and by the differences in renal elimination of TCE (rapid, half-time 10 to 12 hours) and TCA (slow, half-time 50 to 70 hours). In blood, both metabolites achieve steady-state plateau concentrations (TCE more rapidly than TCA) related to the inspired air concentration of MC and its metabolites. In urine, the TCE/TCA ratio, initially low, rises to a constant daily value. After termination of either acute or chronic exposure, the ratio of the amounts of daily urinary metabolites, TCE/TCA (mg/day), is highest 24 hours after exposure. Thereafter, it progressively decreases daily to less than unity by the 5th or 6th day postexposure because of the relatively rapid renal elimination of TCE and the slow renal elimination of TCA (Stewart, 1969; Eben and Kimmerle, 1974; Monster, 1979).

The profile of TCE and TCA urinary excretion during and after MC exposure is similar to that observed for trichloroethylene (Nomiyama and Nomiyama, 1971; Muller et al., 1974; Sato et al., 1977; Monster et al., 1976, 1979a;

Fernandez et al., 1977). However, the ratio of TCE/TCA excreted is 2-fold greater for MC than for trichloroethylene, suggesting differences in the pathways and rates of metabolism to TCE and TCA for these two chlorinated hydrocarbons. Trichloroethylene, a chlorinated olefin, is thought to be metabolized by hepatic microsomes to an epoxide, then to chloral hydrate, and thence to TCE and TCA (Liebman and Ortiz, 1977; Henschler, 1977; Van Duuren, 1977). However, neither epoxide nor chloral hydrate have been identified as metabolites of MC. Comparison of the percentage of the body dose metabolized to TCE and TCA (MC, 3-6 percent vs. trichloroethylene, 80-90 percent) explains the 25- to 30-fold difference in the total amounts of these metabolites (mg/day) excreted into urine for comparable body doses retained after inhalation exposure (Seki et al., 1975; Stewart, 1968; Stewart et al., 1969; Monster, 1979; Ikeda and Ohtsuji, 1972; Ikeda et al., 1972). In a comparative study of rats exposed to 200 ppm (1,080 mg/m^3) MC or its 1,1,2-isomer, Ikeda and Ohtsuji (1972) reported that the urinary excretion of total chlorinated metabolites was substantially less for the 1,1,2-isomer, indicating that the 1,1,2-isomer is metabolized to an even smaller extent than MC. These workers determined the urinary metabolites of the 1,1,2-isomer as TCE and TCA by a spectrophotometric method based on the Fujiwara reaction. However, the MC isomer requires a shift of a chlorine atom from one carbon to the other in order to form TCA or TCE, an unlikely reaction _in vivo_ for a saturated aliphatic, and it is probable that dichlorometabolites were actually measured. Yllner (1971) injected ^{14}C-labeled 1,1,2-trichloroethane, i.p., into mice. Over a 3-day period, 73 to 87 percent of the activity was recovered in the urine, less than 2 percent in the feces. Expired air contained 16 to 22 percent of the radioactivity (60 percent $^{14}CO_2$ and 40 percent unchanged parent compound). From 1 to 3 percent remained in the animal. This indicates that the metabolism of 1,1,2-trichloroethane is significantly greater than MC.

4.2.3 Enzyme Pathways of Methyl Chloroform Metabolism

The metabolic pathways and enzyme mechanisms for the metabolism of halogenated hydrocarbons assume considerable importance for understanding and assessing cellular toxicity. Compounds that in the course of their metabolism form intermediates reactive with cellular macromolecules, e.g., epoxides or free radicals, are associated with enhanced cellular toxicity and carcinogenic potential (Van Duuren, 1977). In comparison with other halogenated hydrocarbons, MC is not extensively metabolized by mammalian systems; this may explain, in part, its lower toxicity and carcinogenic potential (Weisburger, 1977).

Figure 4-3 summarizes the presently postulated enzyme steps in the biotransformation of MC to TCE and TCA, the only known metabolites appearing in the plasma and urine of animals and man (Table 4-6). It is assumed that metabolism occurs principally in the liver, although *in vitro* experiments that directly demonstrate and evaluate MC metabolism by the liver have only been reported for TCE production (Ivanetich and Van Den Honert, 1981).

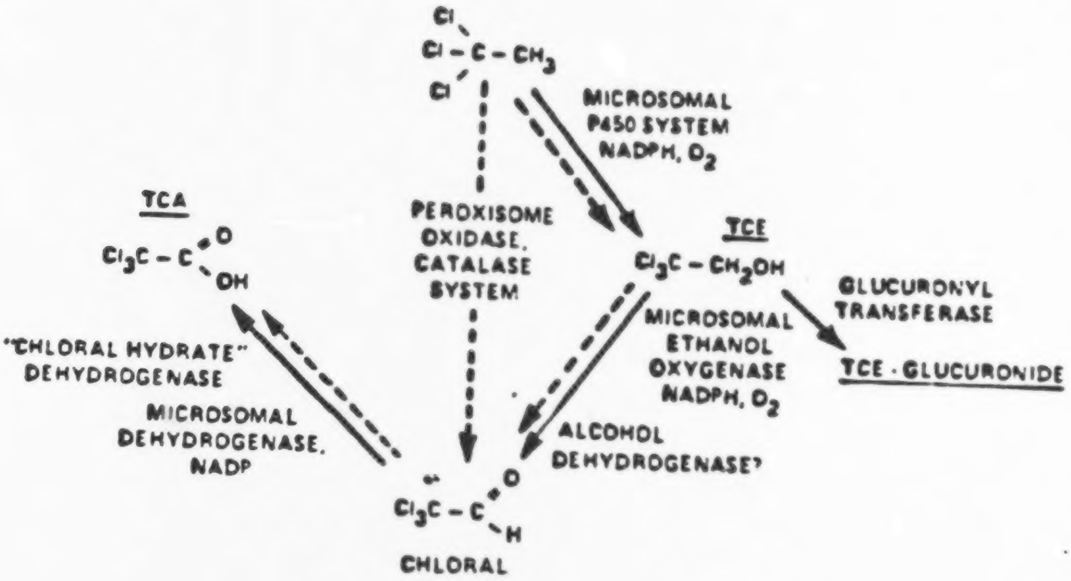
TCA
TCE
MICROSOMAL P450 SYSTEM NADPH, O2
PEROXISOME OXIDASE, CATALASE SYSTEM
GLUCURONYL TRANSFERASE
TCE · GLUCURONIDE
MICROSOMAL ETHANOL OXYGENASE NADPH, O2
ALCOHOL DEHYDROGENASE?
"CHLORAL HYDRATE" DEHYDROGENASE
MICROSOMAL DEHYDROGENASE, NADP
CHLORAL

Figure 4-3. Postulated pathways of hepatic biotransformation of MC. (Davidson, 1980 and Ivanetich and Van Den Honert, 1981.)

Schumann et al. (1982a), using ^{14}C-MC studied the routes of elimination in both rats and mice. Hake et al. (1960), found that about 0.5 percent of the dose (of the 2 percent metabolized; see Table 4-7) was converted to $^{14}CO_2$, following 1,1,1-trichloroethane-1-^{14}C administration (intraperitoneal) to rats, suggesting carbon-carbon cleavage. The origin of the $^{14}CO_2$ is an open question since both Schumann et al. (1982a) and Hake et al. did not identify the source. The ^{14}C-MC used by Hake et al. was contaminated with trace amounts of the MC isomer 1,1,2-trichloroethane-1-^{14}C (0.4 percent) and 1,1-dichloroethane-1-^{14}C (0.5 percent). Both of these compounds were reported by Van Dyke (1971, 1977) to be readily dechlorinated by the rat liver microsomal P450 system. The optimal configuration for dechlorination was a dichloromethyl group. Hence, 1,1,2-trichloroethane, the more toxic isomer, was readily dechlorinated but 1,1,1-trichloroethane was not. For the isomer 1,1,2-trichloroethane, the products were identified as mono-and dichloroethanol and mono- and dichloroacetic acid (Van Dyke and Wineman, 1971), which are known to be metabolized to CO_2 or to form glutathione conjugates (Yllner, 1971a,b). Carlson (1973) found that pretreatment of rats with phenobarbital, but not methylcholanthrene, potentiated hepatotoxicity (measured as serum SGOT and SGPT) of both inhaled MC and its 1,1,2-isomer, but the toxicity of the isomer was increased to a far greater extent. These several observations suggest that 1,1,2-trichloroethane, but not MC, may be extensively metabolized by the oxidative dechlorination system of Van Dyke and Wineman (1971).

Figure 4-3 proposes that the initial pathway of MC transformation is hydroxylation of MC to TCE by the microsomal P450 mixed function oxidase system (Ivanetich and Van Den Honert, 1981). There are several other observations which support this postulation.

First, when MC is incubated aerobically with rat liver microsomes plus NADPH, it produces a P450 type I binding spectrum with peaks at 452 nm and 420 nm, and a reduced spectrum with a peak at 420 nm only (Cox et al. 1976; Pelkonen and Vainio, 1975).

Secondly, MC inhalation induces the P450 drug metabolizing system (Fuller et al., 1970; Lal and Shah, 1970). Rats exposed to inhaled MC (2500 to 3000 ppm; 13,500 and 16,200 mg/m^3) continuously for 24 hours exhibited decreased hexobarbital sleeping time, and decreased duration of effect of meprobamate and zoxazolamine. Furthermore, liver microsomes from MC-pretreated rats exhibited increased in vitro metabolism of hexobarbital, zoxazolamine, and aminopyrine, type I substrates. Livers from pretreated rats had increased cytochrome P450 and NADPH cytochrome C reductase activity, preventable by cycloheximide or actinomycin D. This induction of hepatic microsomal drug metabolism in the reports of Fuller et al. (1970) and Lal and Shah (1970), suggests the possibility that MC might induce its own metabolism with repeated daily exposure. However, the observations of Platt and Cockrill (1969) and Schumann et al. (1982b) argue against this. Platt and Cockrill (1969) reported MC to be essentially without effect in enhancing the hepatic MFO system of mice orally exposed to 1,650 mg/hg/day for 7 days. As previously discussed in this chapter, Schumann et al. (1982b) found that repeated exposure of rats and mice to 1,500 ppm (8,100 mg/m^3) for 16 months did not significantly affect the disposition of MC compared to singly exposed rats and mice. Stewart et al. (1969) observed that men experimentally exposed to 500 ppm (2,700 mg/m^3) MC for 7 hours, for 5 days excreted in their urine progressively increased daily amounts of TCE and TCA although the daily ratio TCE/TCA remained relatively constant (2.8). Eben and Kimmerle (1974) found that rats exposed daily to 204 ppm (1,101 mg/m^3) MC (8 hr/day 5 day/wk) for 14 weeks excreted progressively increasing amounts of TCE for the first few weeks. The TCE/TCA ratio increased to a maximum (about 20) that was maintained for the remainder of the 14-wk exposure period.

Thirdly, MC can interact with pathways of drug metabolism. Plaa et al. (1958) and Shah and Lal (1976) found that MC given intraperitoneally to mice (1 mg/kg) potentiates pentobarbital sleeping time and reduces hexobarbital metabolism by liver microsomes. This observation, in contrast to induction of metabolizing enzymes by inhalation exposure or by intraperitoneal administration in oil, is explained on the basis of different amounts of MC reaching the liver by the various routes and methods of administration. Van Dyke and Rikans (1970) added MC directly to rat liver microsomes incubated in vitro. They observed no effect on N-demethylation of aminopyrine, but a 50 percent increase of aniline 4-hydroxylation, a type II substrate. The 1,1,2-isomer produced similar results.

The origin of TCA as a plasma and urinary metabolite of MC is postulated to occur from enzymic oxidation of TCE. TCE-glucuronide, also present in plasma and urine, is presumed to be formed by glucuronyl transferase. TCE, exogenously administered to man, yields TCA as a metabolite (Marshall and Owens, 1954; Owens and Marshall, 1955a,b; Muller et al., 1974). Marshall and Owens (1954) also observed TCA formation during TCE incubation with rat or dog liver slices. The most likely reaction for the oxidation of TCE to TCA would involve the enzyme alcohol dehydrogenase (Figure 4-3). However, in vitro studies with alcohol dehydrogenase purified from horse liver, and with rat liver cytosol fractions, have shown that TCE is a poor substrate for alcohol dehydrogenase and that significant conversion to trichloroacetaldehyde (chloral) does not occur (Sellers et al., 1972; Friedman and Cooper, 1960; Marshall and Owens, 1954). The reverse reaction --reduction of chloral to TCE -- proceeds rapidly with a K_m of 2.7×10^{-3}M for horse liver enzyme (Butler, 1948, 1949; Marshall and Owens, 1954, 1955a,b; Friedman and Cooper, 1960; Sellers et al., 1972). Also, chloral hydrate has been sought, but not detected, as an intermediate metabolite in plasma of rats and man exposed by inhalation to MC (Monster et al., 1979; Eben and Kmmerle, 1974). On the other hand, chloral hydrate exogenously administered is very rapidly metabolized in vivo with a half-life of only a few minutes, yielding both TCE and TCA as metabolites in plasma and urine (Butler, 1948; Marshall and Owens, 1954, 1955a,b; Breimer et al., 1974; Muller et al., 1974; Cole et al., 1975).

The conversion of chloral to TCA is usually ascribed to so-called "chloral hydrate dehydrogenase," a substrate-specific NAD-dependent enzyme described by Cooper and Friedman (1958). This enzyme was obtained from rabbit liver acetone powders. Cooper and Friedman reported that acetaldehyde was not a substrate, but rather a markedly effective inhibitor; they did not demonstrate a normal endogenous substrate. Human cytosolic acetaldehyde dehydrogenase does not convert chloral hydrate to TCA (Kraemer and Deitrick, 1968; Blair and Bodley, 1969; Sellers et al., 1972). Grunnet (1973) reported that chloral hydrate is not a substrate for mitochondrial NAD-dependent acetaldehyde dehydrogenase. Microsomal NADP-dependent acetaldehyde dehydrogenases with broad substrate specificity have been described, but whether chloral hydrate is a substrate has not been determined (Tottmar et al., 1973).

There is little evidence which precisely defines the enzymatic pathways for the metabolism of MC to TCE by P450 mixed function oxidase system, and TCE to TCA by classical alcohol dehydrogenase and acetaldehyde dehydrogenase enzymes. Although as yet uninvestigated, it is possible that TCE may be a substrate for the microsomal P450 ethanol oxidative system (MEOS) described by Lieber and his coworkers for ethanol and other alcohols (Lieber and De Carli, 1969; Teschke et al., 1977). TCE has been shown by Uehleke et al. (1976) to give a binding spectrum with rat microsomes. An alternative pathway also uninvestigated is afforded by the peroxisomal oxidase-catalase system (Figure 4-3), which is known to readily oxidize ethanol and a broad spectrum of other substrates (Masters and Holmes, 1979; Chance et al., 1977). Indeed, peroxisomes may perhaps be involved in the initial oxidation of MC to TCE and other halogenated hydrocarbons as well.

4.3 SUMMARY AND CONCLUSIONS

The pharmacokinetics and metabolism of MC in man have been studied less than other chlorinated aliphatic solvents, both in controlled experimental conditions and in the workplace. Like other solvents of this group, inhalation and lung absorption of MC vapor in the air is the most important and rapid route of absorption into the body. Absorption through the skin by direct liquid contact is slow and adds less than 5 percent to total body dose. At the accepted TWA value (350 ppm; 1,890 mg/m^3) for an 8-hr exposure, less than 2 g may be expected to be absorbed into the body of a normal 70 kg man. This is because pulmonary absorption is directly related to the blood/air partition coefficient, which for MC is less than that of most other structurally related solvents. MC total body dose increases in direct proportion to inspired air concentration until steady-state is reached; it is also increased by physical activity during exposure. MC distributes throughout the body, readily crossing the blood-brain barrier and probably the placental barrier as well. It can be assumed that MC also distributes into the colostrum or milk of nursing mothers, although no specific data are available. Relative body tissue concentrations are not known, but there is a high affinity for adipose tissue due to the higher lipid/ blood partition coefficient of MC compared with that of other related solvents. Blood and tissue concentrations achieved at equilibrium are directly proportional to inspired air concentration.

MC is metabolized in man to a very limited extent--no more than 6 percent of the total body dose. Metabolism appears to occur principally in the liver, and to an unknown extent in other tissues, yielding only trichloroethanol (TCE) and trichloroacetic acid (TCA) as identified metabolites. Urinary excretion of these metabolites is proportional to inspired air concentration and the total body dose of MC. Detailed information concerning the enzymatic pathways of metabolism is lacking at low concentrations. However, at high concentrations (1,500 ppm), the biotransformation of MC appears to be a saturable, dose-dependent process. The importance of greater knowledge of the biochemical mechanisms and pathways of metabolism relates to awareness that "reactive intermediate" metabolites may contribute to tissue and organ toxicities as well as carcinogenic potential. The mechanism(s) of the initial biotransformation of MC to TCE, where "reactive intermediates" may occur, are speculative, although present evidence suggests a microsomal cytochrome P450 oxidative reaction. However, specific covalent binding studies which may help confirm reactive intermediates have not been carried out. Also, other minor pathways and unidentified metabolites have not been identified. Metabolism is enhanced by microsomal inducers such as phenobarbital and although self-induction by MC does not appear likely, the interaction of MC metabolism and toxicity with other common drugs, including ethanol, has not been adequately investigated.

During post-exposure, between 80 to 90 percent of MC is excreted unchanged by the lungs. Alveolar air concentration and blood concentration decline in a parallel exponential fashion exhibiting three major components of elimination with half-times of approximately 1, 9, and 30 hours. The long half-time of elimination (30 hours) is related to elimination from adipose tissue. Further research on the disposition and fate of MC after low chronic vapor exposures would be helpful, particularly with respect to bioaccumulation, enzyme mechanisms of biotransformation, and interactions with common drugs.

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5. TOXIC EFFECTS

Since its commercial introduction in 1954, methyl chloroform has been used increasingly as an industrial solvent and in consumer products. Usually the most important path of entry into the body is by inhalation. The principal health effect of over-exposure is upon the central nervous system. While thresholds for such effects are difficult to characterize, levels around 1,000 ppm (5,400 μg/m^3) may result in coordination problems. At much higher levels, anesthesia becomes apparent and death may occur at 1 to 3 percent due to anesthesia and/or cardiac toxicity. Unlike other chlorinated hydrocarbons, MC has not been associated with clearly evident liver or kidney damage. The available literature on the possible toxic effects of MC is reviewed in this chapter.

5.1 HEALTH EFFECTS IN HUMANS

5.1.1 Experimental Studies

Experimental studies in humans have centered around three general areas: clinical experiences with MC as an anesthetic; the kinetics of MC absorption and excretion after exposure via the inhalation and cutaneous routes; and the impairment of psychophysiological functions in humans exposed to MC.

Dornette and Jones (1960) administered MC to 50 patients undergoing elective surgery. Nitrous oxide-oxygen (4:1) was used as the vehicle and as a supplemental anesthetic agent. The concentration of MC required for induction of surgical plane anesthesia varied from 10,000 to 26,000 ppm (54,000 to 140,400 mg/m^3), and for maintenance of light anesthesia from 6,000 to 22,500 ppm (32,400 to 121,500 mg/m^3). Rapid induction and recovery, analgesia, and the absence of disagreeable odor, respiratory depression, postoperative depression, nausea and vomiting were listed as advantages in the use of MC. A definite disadvantage was depression of blood pressure during anesthesia of moderate depth. The tendency to develop ventricular arrhythmias during hypoxia was also observed but this effect was reversed when effective oxygenation was reestablished.

Cardiac sensitization from exposure to high concentrations of halogenated hydrocarbons, with resultant increased susceptibility of the heart to catecholamine-produced arrhythmias, e.g., ventricular fibrillation or ventricular tachycardia, is a well-known phenomenon. This topic has been comprehensively reviewed by Aviado et al (1976). Clark and Tinston (1973) believe that cardiac sensitization caused by these relatively inert, lipid soluble hydrocarbons is very likely to be a structurally non-specific action on myocardial membranes by solution and distribution within these membranes, and is, therefore, an example of "physical toxicity" (see Sect. 5.2.3). From an evaluation of 14 halogenated hydrocarbons in dogs, Clark and Tinston (1973) found that the cardiac sensitizing potencies, as determined by the partial pressure in inhaled air needed to sensitize the heart to epinephrine, was directly related to their saturation vapor pressures. In a similar way, the anesthetic potency or narcotic action of the halogenated hydrocarbons, a structurally nonspecific action, is directly related to the blood/air or lipid/air partition coefficient for these compounds (Table 4-1) (Miller et al., 1972; Eger et al., 1965; Sato and Nakajima, 1979).

Siebecker et al. (1960) reported that electroencephalographic patterns during MC anesthesia showed little change before circulatory depression and that the changes were similar to those during halothane anesthesia. The investigators found MC to be less potent clinically than either chloroform or halothane in supplementing nitrous oxide-oxygen for anesthesia.

Stewart et al. (1961) evaluated the acute effects of increasing concentrations (0 to 2,600 ppm; 0 to 14,040 mg/m^3) of MC over a 15 minute exposure period. The commercial grade of MC used was Chlorothane®. Table 5-1 shows the subjective and physiological responses during exposure to MC. In another experiment in which 6 subjects were exposed to MC at 500 ppm (2,700 mg/m^3) for 78 minutes or 186 minutes, no eye irritations or dizziness occurred, nor were balance or coordination affected. Exposure at 900 to 955 ppm (4,860 and 5,157 mg/m^3) for 73, 35, and 20 minutes produced a number of psychophysiological effects which are listed in Table 5-2.

In another study, Torkelson et al. (1958) exposed humans to MC (Chlorothane®) vapors. Exposure to 550 ppm (2,970 mg/m^3) for 90 minutes had no measureable effect on the vital signs being monitored. Exposure to 500 ppm (2,700 mg/m^3) for 450 minutes produced no significant changes in pulse, respiration, blood pressure, reflexes, or equilibrium; liver function tests were also negative. Exposure to 1,000 ppm (5,400 mg/m^3) for 30 minutes was also without effect. However, exposure to 900 to 1,000 ppm (4,860 to 5,400 mg/m^3) for 75 minutes resulted in slight eye irritation and a feeling of lightheadedness, and the Flanagan and Romberg tests revealed a slight but definite loss of coordination and equilibrium. ECG and liver function tests were normal. Exposure to 1900 ppm for 5 minutes resulted in an obvious disturbance of equilibrium and a positive Romberg test.

In 1969, Stewart et al. reported that exposure to 500 ppm (2,700 mg/m^3) for periods of 6.5 to 7 hours/day for 5 consecutive days resulted in mild subjective responses (sleepiness, eye irritation, and mild headache). The only untoward physiological response was an abnormal Romberg test. However, the two individuals who had the abnormal response had, according to the authors, demonstrated difficulty performing the test before any exposure. None of the clinical tests performed during or following the exposure were abnormal.

TABLE 5-1. SUBJECTIVE AND PHYSIOLOGICAL RESPONSES TO A CONSTANTLY INCREASING METHYL CHLOROFORM VAPOR CONCENTRATION OVER A PERIOD OF 15 MINUTES

Concentration (ppm)	Responses to Exposure
0 to 1000	Increasing awareness of a slightly sweet, not unpleasant odor.
1000 to 1100	Mild eye irritation noted in 6 of 7 subjects.
1900 to 2000	6 of 7 subjects aware of throat irritation.
2600	1 subject very lightheaded.
2650	2 subjects unable to stand. 3 subjects very lightheaded, but able to stand. 2 subjects were not lightheaded, and one of these was able to demonstrate a normal Romberg test.

Source: Stewart et al. (1961).

TABLE 5-2. SUBJECTIVE AND PHYSIOLOGICAL RESPONSES TO METHYL CHLOROFORM VAPOR CONCENTRATIONS OF 900 TO 1000 PPM

Average Concentration	Responses to Exposure[a]
900 ppm for 20 minutes (3 subjects)	Positive Romberg in one subject. Greater effort required to perform a normal Romberg in two subjects after 10 minutes of exposure. Heel-to-toe walking normal. Two subjects experienced lightheadedness above 900 ppm.
910 ppm for 35 minutes (2 subjects)	Greater mental efforts required to perform a normal Romberg test after 10 minutes of exposure. All heel-to-toe walking performed well. One subject experienced persistent lightheadedness above 900 ppm.
951 ppm for 73 minutes (3 subjects)	Greater mental effort required to perform a normal Romberg test after 10 minutes of exposure. After 15 minutes of exposure one subject had consistently positive Romberg. Heel-to-toe walking performed well by all during exposure. No lightheadedness.

[a] Mild eye irritation was noted by all subjects when vapor concentrations rose above 1000 ppm.

Source: Stewart et al. (1961).

In 1975, Stewart et al. reported an experiment in which 20 subjects were exposed to 500 ppm (2,700 mg/m^3) MC or less for 7.5 hours per day, 5 days per week for 3 weeks. No serious deleterious effects upon health or performance were detected, and the health of the subjects remained unimpaired during the inhalation studies. The blood chemistries, hematologies, urinalyses, electrocardiograms, and pulmonary function tests remained normal. There was a slight increase in the number of reported negative subjective responses (Table 5-3).

Twelve subjects were exposed to 250, 350, 450, and 550 ppm (1,350; 1,890; 2,430; and 2,970 mg/m^3) of MC in inspired air during four continuous 30 minute periods in an experiment reported by Gamborale and Hultengren (1973). The air-gas mixture was supplied via a breathing valve and a mouthpiece with very low resistance. The effects of the introduction of the breathing tube were not assessed. In the final 20 minutes of each exposure period, five performance tests were made. Two of the tests were of perceptual speed and the others were tests of simple reaction time, choice reaction time, and manual dexterity. The same subjects were also studied under control conditions in which inspired air contained no MC but in which all operations and measurements were the same as during exposure to the solvent. The presence or absence of MC was reportedly disguised by the use of menthol crystals. To balance the training effects between experimental and control conditions, the order of conditions was reversed for half the subjects.

The change in mean performance level during exposure to the increasing concentrations of MC differed systematically from the change in performance under control conditions. The level of performance in the manual dexterity test and two perceptual tests were affected by training; however, the training effect was less pronounced during exposure to MC. The tests of reaction time were less sensitive to training and, with these, there was an absolute decline in performance capability as the exposure concentration increased. However, this study contained several drawbacks: e.g., the substance used to disguise the MC odor may itself have had a toxic effect, and the introduction of a breathing tube may have induced stress in the subjects. Statistically significant performance differences between experimental and control conditions were reported for all tests with exposure levels of 350 ppm (1,890 mg/m^3) or greater, but the authors used repeated-test strategies. Such tests usually yield more significant results than warranted (Benignus and Muller, 1982).

Salvini et al. (1971) evaluated psychophysiological effects after exposing six male university students to an average vapor concentration of 450 ppm (2,430 mg/m^3) MC for two periods of 4 hours, separated by a 1.5 hour interval. During exposure they alternated their activities with a one-hour study period followed by 20 minutes of physical excercise. Each subject was examined on two different days using a crossed-scheme analysis. The psychophysiological tests included a perception test with tachistoscopic (brief exposure to visual stimuli) presentation, the Wechsler Memory Scale test, a complex reaction time test, and a manual dexterity test. After two exposures, no disturbances in motor function, coordination, equilibrium, or behavior patterns were observed in any of the subjects. However, there were some complaints about eye irritation. The only factor that was reported to be statistically significant was the association between exposure to MC and perception of mental strain. Under mental stress conditions, exposure to 450 ppm (2,430 mg/m^3) MC was reported to have "decreased perceptive capabilities". Mental fatigue was determined by comparing perception test results between the morning and afternoon tests. A small reduction in performance was also observed but was not statistically significant.

Savolainen et al. (1981) evaluated various psychophysiological functions in 9 male students exposed for 4 hours/day, at 6-day intervals, to MC (200 and 400 ppm; 1,080 and 2,160 mg/m^3) and m-xylene (200 ppm) and MC (400 ppm; 2,160 mg/m^3) in combination. Exposure to MC or MC and xylene together were without effect on reaction time, body balance, and critical flicker fusion thresholds.

5.1.2 Occupational Studies

Chronic occupational exposure to other chlorinated solvents has occasionally been reported to cause adverse neurological and behavioral effects. Based on the absence of effects at 500 ppm (2,700 μg/m^3) in the better conducted human studies, relatively low level ambient exposures to MC would not be associated with adverse neurological and behavioral effects.

A recent attempt to assess the central and peripheral nervous system effects of MC in occupational situations was undertaken by Maroni and coworkers (1977). They studied a very small group (22 subjects) of female workers exposed to MC vapors at concentrations ranging from 110 to 990 ppm (594 to 5,346 mg/m^3). When compared to workers who were reportedly unexposed, no differences were found in clinical symptoms or measures of nerve conduction velocity and psychometric function.

In another study, Seki et al. (1975) surveyed 196 male workers employed in four Japanese printing factories where MC was the sole organic solvent in use. The four groups of workers were exposed to average concentrations of 4, 25, 28, and 53 ppm (22, 135, 151, and 286 mg/m^3). The workers participated in a medical interview coupled with a test for sense of vibration (studied at the distal joints of the thumbs and great toes using a 128 Hz tuning fork) as well as routine laboratory examinations, including peripheral hemograms, determination of blood specific gravity, and urinalysis for urobilinogen and protein. These examinations revealed no consistent dose-related adverse effects among the four groups of workers.

In the most recent study, Kramer et al. (1978) measured numerous physiological parameters of workers in two adjacent textile plants. Detailed blood chemistry and hematology studies were conducted for 151 matched pairs of employees to compare the exposed and unexposed partners. All employees in the exposed group had been exposed to MC (and other solvents), in varying concentrations, for up to 6 years. The concentration range was 11 to 838 ppm (59 to 4,525 mg/m^3), with a mean of 115 ppm (621 mg/m^3) MC. It is questionable whether this period of exposure would result in toxic symptoms. Because only healthy, active workers were selected, and the average length of exposure for the study population was less than 1 year at the stated TWA, no conclusions can be drawn about accumulative, long term effects. The control group was only minimally exposed to nonchlorinated solvents.

Pairs were matched with regard to age, race, sex, work shift, job description and socioeconomic status, and examined within a 10 week period. Subject height, weight, blood pressure and pulse were obtained, and electrocardiograms were recorded. Laboratory blood determinations included hematocrit, hemoglobin, red blood cell count (RBC), white blood cell count (WBC), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV) alkaline phosphatase, SGOT, SGPT, gamma glutamyl transpeptidase, total bilirubin, urea nitrogen, LDH, uric acid, total protein, A/G ratio, albumin, calcium, and phosphorus. For quantitative variables, t tests and tests of homogeneity of variance were made. Multiple regression analysis was performed on paired differences with respect to environmental variables and on the combined matched exposed and control populations with respect to demographic variables.

Breathing zone samples were collected in charcoal tubes, except in a few locations where area sampling was more practical, and analyzed on a portable gas chromatograph equipped with a flame ionization detector. Samples of expired air were analyzed immediately after collection by gas chromatography.

After explaining that some data were eliminated on the basis of subjects' smoking habits, high blood pressure, or prior illness, the authors presented statistical findings but no individual data. MC concentrations in the breath ranged from "less than 5 ppm" to "greater than 30 ppm," with the majority (127/151) between 5 and 29 ppm (27 and 157 mg/m^3). Comparison of the health test data between exposed and control subjects revealed no statistically significant differences except in a decrease in SGPT in the exposed group and a slight increase in abumin in the exposed group. The authors concluded that no health impairment was suffered by workers exposed to an average daily concentration of 115 ppm (621 mg/m^3) MC.

5.1.3 Accidental Exposure

Accidental exposure to excessive concentrations MC can lead to death. Table 5-3 lists the signs and symptoms of a number of cases in which the patients survived. These results suggest that MC has only a minimal potential for producing liver or kidney injury in man upon acute exposures. The primary toxic effect appears to be a reversible depression of the CNS, typical of an anesthetic agent. While abuse or misuse of any organic solvent has been difficult to control, the problem has diminished in recent years. The following is a review of some of the acute exposure incidents related to MC but where no exposure measurements were possible.

Two fatal cases in which the subjects intentionally inhaled cleaning fluids containing MC were reported by Hall and Hine (1966). A 19-year-old woman who was observed sniffing cleaning fluid over several days and acting irrationally was later found dead.

There were indications of chronic, intentional inhalation of a cleaning fluid containing MC in the other fatal case studied by Hall and Hine (1966). On autopsy, pathologic findings were confined to the respiratory system and the kidneys. The lungs were congested and edematous, the vessels dilated, and small hemorrhagic areas were present. The kidneys showed marked vascular congestion around the pyramids, especially on the periphery.

In neither of these cases were drugs or solvents detected in the stomach contents, and no barbiturates were found in the blood. Blood levels of MC were 72.0 and 13.0 mg percent, respectively.

Twenty-nine cases of presumed sudden death from sniffing MC during 1964 to 1969 were reported by Bas (1970). These were among 110 cases of sudden death attributed to sniffing volatile hydrocarbons and halocarbons summarized by the author. In 18 of the 110 cases, death followed sniffing coupled with some form of exercise. No anatomical abnormalities were found from gross or

TABLE 5-3. SIGNS AND SYMPTOMS OF PATIENTS SURVIVING INTOXICATION WITH METHYL CHLOROFORM

Reference	Patient	Amount	BP[a]	HR[b]	SGPT[c]	SGOT[d]	AP[e]	BUN[f]	ECG[g]	Comments
Stewart and Andrews, 1966	47 M	1 oz. orally	120/80	84	N[h]	N	NR[i]	N	N	No abnormal neurologic findings; proteinuria was 1+; hematocrit 53%; hemoglobin level 18 gm/100 ml
Stewart, 1971	44 WM	Inhalation	140/74	78	N	N	NR	N	N	Neurologic examination revealed abnormal Romberg's sign upon admission; hematocrit 46%; hemoglobin level 14.6 gm/100 ml
Stewart, 1971	55 WM	Inhalation	160/96	84	N	N	NR	N	N	No abnormal neurologic findings
Stewart, 1971	47 WM	Inhalation	160/90	76	N	N	N	N	N	No abnormal neurologic findings
Litt and Cohen, 1969	5 teenage M	Inhalation	NR	NR	NR	340-100 μ	7-30 μ	NR	NR	Nervous system symptoms including paresthesia, tinnitus, ataxia, and headache

[a] Blood pressure (mmHg)
[b] Heart rate (beats/min)
[c] Serum glutamic-pyruvic transaminase
[d] Serum glutamic-oxaloacetate transaminase
[e] Alkaline phosphatase
[f] Blood urea nitrogen
[g] Electrocardiogram
[h] N = normal
[i] NR = not reported

microscopic post mortem examinations that could explain the sudden deaths. The author discussed the possibility that resulted from cardiac sensitization to endogenous catecholamine.

Six fatal cases were reported by Stahl et al. (1969). In the first case, a 20-year-old man was found dead in a closed space in which he had been working with a "paint remover." Gas chromatographic analysis revealed MC in all tissues. Upon autopsy, the lungs were found to be congested and moderately edamatous; the liver, spleen, kidneys, and brain were also congested. Microscopic examination of the brain suggested anoxia as the cause of death.

In the second case, a 17-year-old man was found dead in a room in which he was cleaning an air vent with MC. Gas chromatographic analysis revealed the presence of MC although blood levels were only 0.15 mg percent. At autopsy, the skin was moderately cyanotic, the brain, liver, kidneys, and spleen were moderately congested, and the lungs were markedly edematous with evidence of aspiration of gastric contents. Blood lactic acid levels were high. The authors concluded that death was probably due to O_2 deprivation.

In the third case, an obese 24-year-old man was found dead in bed after having cleaned electrical equipment with MC. At necropsy, marked cyanosis of the head and neck were noted; the lungs were congested and edematous. The brain, spleen, and kidneys were also congested.

In the fourth, fifth, and sixth cases, three males were found dead in an unventilated 4 x 5 ft. compartment where they had been cleaning electrical equipment with MC. Autopsies revealed congestion and edema of the lungs. Blood levels of MC were 12.0 mg percent, 6.2 mg percent, and 6.0 mg percent in these victims.

Hatfield and Maykoski (1970) reported on a 27-year-old who was found dead in an aircraft tank that he had been cleaning with MC. Upon autopsy, the lungs showed some passive congestion and some edema. The kidneys showed some passsive congestion and there appeared to be some slight edema of the brain. Microscopic examination disclosed a pulmonary parenchyma with considerable acute passive congestion and focal extravasations of red blood cells into alveolar spaces. Upon section, the renal parenchyma was intensely congested and of a dark red color. Microscopically, there was intense, acute passive congestion. There appeared to be marked congestion of the small vessels within the white matter of the brain. The diagnosis was acute passive congestion of the viscera with petechial hemorrhages in the lung and brain. Hatfield and Maykoski estimated the concentration level of MC to which this worker was exposed at 62,000 ppm (334,800 mg/m^3).

Caplan et al. (1976) reported a fatal intoxication in which a 40-year-old female was apparently overcome while painting a bathroom. On external examination, the only significant abnormality was in the respiratory system. The bronchi contained frothy fluid. On section, the lungs exuded moderate amounts of frothy fluid. Histologically, the lungs showed acute edema and congestion, and the liver showed a mild fatty change. MC was identified in tissue samples.

Twenty-one deaths assumed to be related to the abuse or gross misuse of decongestant aerosol sprays containing MC in the solvent resulted in removal of several such products from the market (Federal Register 38:21935-36, 1973). As a followup, a Federal Register notice appeared in 1977 (Federal Register, 1977) and discussed this matter. It was stated: "The action concerning trichloroethane for inhalation is being taken because of the lack of safety and effectiveness data available on trichloroethane when it is used as a component of an aerosolized drug product intended to be inhaled by a sick person. The drug products containing trichloroethane implicated with 21 deaths were used as cough suppressants, primarily in infants."

5.2 EFFECTS ON ANIMALS

5.2.1 Acute and Subacute Effects

The LD_{50}'s of MC for various species are found in Table 5-4. Administration of single oral doses yielded LD_{50}'s for laboratory animals ranging from 8.6 gm/kg for guinea pigs to 14.3 gm/kg for rats (Torkelson et al., 1958). The solvent caused slight transitory irritation in the eyes. The toxicity from skin absorption was found to be low, as doses of 4 gm/kg failed to kill any rabbits exposed for 24 hrs. Repeated multiple daily application of 500 mg/kg to the skin of rabbits caused no effect other than reversible local irritation. In other experiments, laboratory animals were exposed repeatedly to 500, 1000, 2000, and 10,000 ppm (2,700; 5,400; 10,800; and 54,000 mg/m^3) in order to establish conditions safe for repeated exposure. Rats, guinea pigs, rabbits, and monkeys were unaffected after 6 months of repeated 7 hour exposures 5 days/week to 500 ppm (2,700 mg/m^3). Female guinea pigs, which were found to be the most sensitive in previous experiments, were able to tolerate 1000 ppm (5,400 mg/m^3) for 0.6 hour/day for 3 months and 2000 ppm

(10,800 mg/m^3) for 0.1 hour/day with no detectable adverse effects. Male rats tolerated exposure to 10,000 ppm (54,000 mg/m^3) for 0.5 hour per day with no organic injury. The effects of MC were shown to be primarily anesthetic, with only a slight capacity to cause reversible injury to the lungs and liver. Based on this work, Torkelson et al. (1958) suggested that the maximum allowable concentration for MC be 500 ppm (2,700 mg/m^3).

In another study, Eben and Kimmerle (1974) exposed rats acutely (4 hours) and subachronically (8 hours/day, 5 times/week for 3 months) to 220 and 440 ppm (1,188 and 2,376 mg/m^3) and 200 ppm (1,080 mg/m^3), respectively. During the periods of exposure, the authors reported that "the animals did not differ in any way from their controls in behavior, appearance, or body weight gain. Hematologic examination performed at the end of the exposure period did not reveal any pathologic abnormalities". Liver and renal function tests and blood glucose were normal. At autopsy, the organs of the exposed rats were normal; organ weights did not deviate significantly from those of the control animals.

Prendergast et al. (1967) repeatedly exposed 15 Sprague-Dawley rats, 15 Hartley guinea pigs, 3 squirrel monkeys, 3 New Zealand albino rabbits, and 2 beagle dogs (8 hour/day, 5 days/week for 6 weeks) to 2200 ppm (11,880 mg/m^3) MC. The same number of animals were exposed continuously for 90 days to 135 ppm and 370 ppm (729 and 1,998 mg/m^3). The repeated exposure to 2200 ppm (11,880 mg/m^3) did not result in any deaths or visible signs of toxicity, although weight loss was observed in rabbits and dogs. The continuous exposure at 370 ppm (1,998 mg/m^3) did not cause any deaths, visible toxic signs, significant growth depression or biochemical, hematologic or pathologic changes. Continuous exposure to 135 ppm (729 mg/m^3) resulted in three deaths but no visible toxic signs or impaired growth in any of the survivors. Autopsy and subsequent histopathologic examination of the experimental animals revealed lung congestion and pneumonitis which may have been severe enough to have caused the deaths of the two rats and the rabbit, but which were not attributed to the exposure.

The acute behavioral and toxic effects of ethanol and inhaled MC alone and in combination have been examined by Woolverton and Balster (1981) on CD-1 albino mice. The animals were exposed to doses of MC ranging to 20,000 ppm (108,000 mg/m^3) for 30 minutes and then tested for behavioral decrements using

TABLE 5-4. ACUTE TOXICITY OF METHYL CHLOROFORM

Reference	Species	Route	Sex	LD_{50} mg/kg	95% confidence limits
Torkelson et al., 1958	rats	oral	M	14,300	12,100 to 17,000
Torkelson et al., 1958	rats	oral	F	11,000	9,500 to 13,000
Torkelson et al., 1958	mice	oral	F	9,700	
Torkelson et al., 1958	albino rabbits	oral	mixed	10,500	9,700 to 11,300
Torkelson et al., 1958	guinea pigs	oral	mixed	8,600	6,100 to 12,200
Takeuchi 1966	SM mice	i.p.	?	2,568	
Priestly and Plaa 1976	CF-1 Swiss mice	i.p.	M	4,008	3,558 to 4,522
Klaassen and Plaa 1969	Sprague-Dawley rats	i.p.	M	5,054	4,389 to 5,586
Torkelson et al., 1958	albino rabbits	dermal	mixed	15,800	
Adams et al., 1950	rats	inhalation	mixed	18,000[1]	
Plaa et al., 1958	Princeton mice	i.p.	M	16,000	12,700 to 21,400
Klaassen and Plaa 1967	Swiss-Webster mice	i.p.	M	5,080	4,140 to 6,010
Klaassen and Plaa 1967	dog	i.p.	M	4,140	
Gehring 1968	Swiss-Webster mice	i.p.	F	4,700	4,320 to 5,110
Woolvertor et al.,	CD-1 mice	inhalation	M	22,240[2]	

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[1] LC_{50} in ppm for 3 hr exposure; 7 hr exposure resulted in a LC_{50} of 14,250 ppm (12,950 to 15,675).

[2] LC_{50} in ppm for 30 min.

the inverted screen test, a test that requires mice to climb to the top of an inverted screen. Lethality was measured at 24 hours. The inverted screen test was scored by counting the number of animals to fall off plus the number on the underside of the screen, expressing these numbers as a percentage. To test the effect of ethanol, animals were first intubated with varying doses of ethanol and then exposed to MC.

At the highest concentration of MC tested for behavioral effects (7,000 ppm; 37,800 mg/m^3), half of the affected mice recovered within 5 minutes after removal from the chamber and all recovered within 60 minutes. In contrast, at the highest dose of ethanol tested (4 g/kg), half of the animals recovered within 180 minutes and 80 percent recovered within 360 minutes. Twelve mice were used for each data point.

The EC50 for MC at 1 minute following a 30 minute exposure was in the range of 4,644 to 5,778 ppm (24,077 to 31,201 mg/m^3). The 24-hour LC50 was in the range of 22,080 to 22,404 ppm (119,232 to 120,981 mg/m^3). For ethanol, the ED50 was in the range of 1.7 to 2.7 g/kg and the 24-hour LD50 was in the range of 7.5 to 8.0 g/kg.

When the combined effect was evaluated, the investigators observed that low doses of ethanol and MC resulted in a greater-than-additive response both on behavioral and lethal endpoints; higher doses of ethanol were additive or less-than-additive with MC. In general, the LC50/EC50 ratio of MC increased as the dose of ethanol increased (from 0 to 2.0 g/kg). One anomalous finding was at the ethanol dose level of 0.25 g/kg. In contrast to the potentiating effect of ethanol at other dose levels, this dosage increased the EC50 for MC, in comparison and reduced the LC50/EC50 ratio for MC. This dosage of ethanol was not reported to have effects of its own on the parameters measured but apparently decreased the effects of MC. The combined effects data are shown in Table 5-5. Additional information is discussed in section 5.2.2.

Because the liver is a target organ for many chlorinated hydrocarbons, the effects of MC on hepatic function have been studied by a number of different investigators. Lal and Shah (1970) exposed Swiss-albino, random-bred male mice to 3000 ppm (16,200 mg/m^3) for either 24 hours or for 4 or 8 hour/day for several days. Hexobarbital (80 mg/kg)-, barbital sodium (275 mg/kg)- or chloral hydrate (350 mg/kg)-induced sleeping time was measured at predetermined times after exposure. In addition, hexobarbital oxidizing activity, nitro-group

TABLE 5-5. COMPARISON OF LETHAL AND BEHAVIORAL EFFECTS OF MC IN COMBINATION WITH ETHANOL

Ethanol dose (g/kg)	MC LC50 (ppm)	MC EC50 (ppm)	LC50/EC50
0	22,241	5,173	4.3
0.125	20,273	3,834	5.3
0.25	19,852	6,006	3.3
0.5	19,067	3,157	6.0
1.0	17,924	2,200	8.1
2.0	16,834	618	26.5

Source: Woolverton and Balster, 1981

reducing activity, and the protein content of the liver supernatant fraction were also determined. Inhalation of MC at a concentration of 3000 ppm (16,200 mg/m^3) for 24 hours produced a maximum reduction in the duration of hexobarbital sleeping time but had no effect on hypnosis produced by barbital or chloral hydrate. Hypnosis returned to the control level at 48 hours after the termination of exposure. Repeated short exposures, 4 or 8 hour/day for several days, had a cumulative effect, but a single 8 hour exposure did not. The supernatant fraction isolated (9000 g) from livers of mice previously exposed to MC oxidized hexobarbital more efficiently, but the ability to reduce p-nitrobenzoic acid remained unaffected. The protein content of this liver supernatant fraction was also unaltered.

Fuller et al. (1970) made further observations on Lal and Shah's investigations of the inductive effect of MC on hepatic drug metabolism. Male Sprague-Dawley rats and Swiss-albino, random-bred mice were exposed to MC (2500 to 3000 ppm; 13,500 to 16,200 mg/m^3) in a dynamic chamber for 24 hours. Loss of righting reflex due to hexobarbital (120 mg/kg), meprobamate (300 mg/kg), or zoxazolamine (80 mg/kg) administration and in vitro activity of hexobarbital oxidase, zoxazolamine hydroxylase, aminopyrine demethylase, reduced nicotinamide adenine dinucleotide phosphate (NADPH) cytochrome c reductase, and CO-binding pigment (cytochrome P-450) were then measured.

Pretreatment with inhibitors of protein synthesis (cycloheximide and actinomycin D) were used to block the effect of MC on the hepatic drug-metabolizing system. Inhalation of MC (2500 to 3000 ppm; 13,500 to 16,200 mg/m^3) for 24 hours decreased the duration of action of hexobarbital, meprobamate, and zoxazolamine. This was accompanied by an increase in the metabolism of hexobarbital, zoxazolamine and aminopyrine in vitro by hepatic microsomal enzymes. Cytochrome P-450 and cytochrome c reductase were also increased; however, liver weight and liver microsomal protein were not enhanced. Pretreatment of rats with protein synthesis inhibitors prevented the MC induced decrease in hexobarbital sleeping time and the increase in hepatic drug metabolism. The authors "suggest that the increase in drug metabolizing enzymes after methylchloroform inhalation consisted of an induction of new enzyme protein. Since this induction occurs after exposure to concentrations of methylchloroform which do not produce histologically detectable lesions in the liver of rats, it may offer a sensitive prepathologic measure of methylchloroform toxicity."

Savolainin et al. (1977) investigated the effects of MC on rat brain and liver after intermittent inhalation. Ten male Sprague-Dawley rats were exposed to 500 ppm (2,700 mg/m^3) MC for 4 days, 6 hours daily. The right cerebral hemispheres were homogenized and analyzed for protein, RNA, glutathione, and for the activity of acid proteinases. Liver microsomes were analyzed for the amount of protein and for cytochrome P-450 content. MC decreased the liver microsomal cytochrome P-450 content after cumulative exposure to the material for 5 days. The authors explained the decrease in cytochrome P-450 by the previously observed (Pelkonen and Vainio, 1975) affinity of MC for the type I binding site.

McNutt et al. (1975) demonstrated hepatic lesions in mice after continuous inhalation exposure to MC. CF-1 mice were exposed to 0, 250, or 1000 ppm (0, 1350, or 5400 mg/m^3) MC continuously for up to 14 weeks with a weekly serial sacrifice. At 1000 ppm (5,400 mg/m^3), from 1 to 14 weeks, significant changes in centrilobular hepatocytes were observed. Moderate liver triglyceride accumulation was evident in the 1000 ppm (5,400 mg/m^3) group and peaked at 40 mg/gm of tissue after 7 weeks of exposure (by 14 weeks the triglyceride level had not decreased to 16 gm). Electron microscopic evaluation revealed that cytoplasmic alterations were most severe in centrilobular hepatocytes in the 1000 ppm group and were mild to minimal in the 250 ppm group. The alterations consisted of vesticulation of the rough endoplasmic reticulum, with loss of attached polyribosomes, and increased smooth endoplasmic reticulum, microbodies, and triglyceride droplets. Necrosis of individual hepatocytes occurred in 40 percent of the mice exposed to 1000 ppm (5,400 mg/m^3) for 12 weeks. This necrosis was associated with an acute inflammatory infiltrate and hypertrophy of Kupffer cells. This was not evident in mice exposed to 250 ppm (1,350 μg/m^3) and fat accumulation was not elevated above control values. The toxic effects of MC at 1,000 ppm (5,400 μg/m^3) were of a similar type to those produced by carbon tetrachloride, but they appeared to be much less severe. Such effects were not observed at 250 ppm (1,350 μg/m^3).

Table 5-6 shows the relative hepatotoxic effect of MC in comparison to other chlorinated solvents. MC, according to Plaa et al., (1958), was judged to be the least hepatotoxic of the seven solvents investigated.

TABLE 5-6. THE RELATIVE HEPATOTOXIC EFFICACY OF CHLORINATED SOLVENTS

Compound	Relative hepatotoxic efficacy
1,1,1-trichloroethane	1
Tetrachloroethylene	3
Trichloroethylene	8
Sym-tetrachloroethane	12
1,1,2-trichloroethane	40
Chloroform	60
Carbon tetrachloride	190

Adapted from Plaa et al., (1958).

5.2.2 Nervous System and Behavior

There have been few animal studies of the effects of MC on the nervous system and behavior. In the animal studies that have been performed, effects of MC were either not observed or were observed at exposure levels of 4,000 ppm (21,600 mg/m^3) or greater. The effects were upon motor abilities (Woolverton and Balster, 1981), vestibular control (Larsby et al., 1978) or on fixed-interval response rate (Moser and Balster, 1982). Studies apparently have not been performed upon such behaviors as learning or extinction, accuracy or efficiency of complex schedule-controlled behaviors or sensory discriminations. The endpoints that have been evaluated were studied in only a preliminary manner. Nervous system electrophysiology, neurochemistry, and neuropathology are other areas that warrant attention.

Exposure of 10 Sprague-Dawley male rats to 500 ppm (2,700 mg/m^3) was not found to significantly affect activity level. Rats were exposed by inhalation for 4 days, 6 hours/day. They were evaluated one and 17 hours after the last exposure in an open field setting. Ambulation, grooming, rearing, defecation, and urination were measured (Savolainen et al., 1977).

York et al. (1982) reported that exposure of female Long-Evans rats by inhalation before and/or during pregnancy to 2,100 ppm (11,340 mg/m^3) did not affect mating (anecdotal data) nor were open field activity, running wheel rates affected in the offspring. Open field tests were done on post-partum day 21 and running wheel tests from day 21 through day 110. Amphetamine administered to all groups before testing on days 110 through 120 did not alter running wheel rates with respect to controls.

Woolverton and Balster (1981) showed a concentration-related increase in the percent of CD-1 mice affected by MC inhalation on an inverted-screen climbing test. The EC50 for the 12 mice evaluated was about 5,200 ppm (28,080 mg/m^3). At a level of 7,000 ppm (37,800 mg/m^3), about 80 percent of the mice were affected. Tests were run beginning one minute after the termination of exposure. Ethanol doses, given prior to MC exposure, shifted the concentration-effects curve to the left by amounts depending upon MC concentration. It is quite possible that the observed decrements were due to vestibular rather than motor deficits.

The fixed interval response rate in adult male CD-1 mice was measured during inhalation exposure to 1,000, 2,000, 4,000, and 8,000 ppm (5,400, 110,800, 21,600, and 43,200 mg/m^3) MC (Moser and Balster, 1982). Response rate was reduced proportional to concentration in about 5 minutes after the initiation of exposure, beginning at 4,000 ppm (21,600 mg/m^3). It was unclear whether mice were trained in unexposed conditions.

An apparent disturbance in vestibular function due to MC was reported in rabbits by Larsby et al. (1978). MC was infused intravenously and the blood level of MC was monitored. At 75 ppm (405 mg/m^3), rabbits began showing nystagmus during axial body tilts. A crude estimate made from the data reported by Astrand et al. (1973) indicated that 75 ppm (405 mg/m^3) MC in human arterial blood would result upon inhalation of air containing about 4,000 ppm (21,600 mg/m^3).

Protein and RNA content in the brains of Sprague-Dawley male rats at 0, 2, 3, 4, and 6 hours after the last exposure to 500 ppm (2,700 mg/m^3) MC for 4 days, 6 hours/day was measured by Savolainen et al. (1977). No effects were significant after Bonferroni correction for repeated t-tests (Benignus and Muller, 1982).

The available information indicates that, at high levels, MC acts as a CNS anesthetic and at somewhat lower levels it has CNS depressant effects. Until more pertinent information is available, very few conclusions about threshold effects are warranted.

5.2.3 Cardiovascular Effects

The cardiovascular effects produced by exposure to MC have been extensively studied in recent years. Halogenated alkanes, like many organic solvents, have been shown to sensitize the heart to catecholamines and at the same time produce cardiac depression.

Krantz et al. (1959) were the first to observe the cardiac depression produced by MC. Rats were deeply anesthetized with MC for 1 hour, at which time the hearts were immediately removed. Cardiac ventricular slices were promptly prepared and the oxygen uptake over the 1 hour period was measured. MC anesthesia was associated with a significant diminution (33.3 percent) in oxygen uptake of the myocardium. Blood pressure studies in dogs also revealed that anesthesia with MC elicited a depressed response. At the point of respiratory arrest, the blood pressure was reduced to approximately one-half its normal value. Ether anesthesia under similar conditions results in only a slightly depressed blood pressure. Six dogs and two rhesus monkeys were anesthetized and electrocardiograms recorded. The pattern of the electro-

TABLE 5-7. NERVOUS SYSTEM AND BEHAVIORAL EFFECT OF MC IN LABORATORY ANIMALS

REFERENCE	SPECIES	SEX	EXPOSURE	EFFECTS
Savolainen et al. (1977)	Sprague-Dawley rats	Male adults	Inhalation 500 ppm, 4 days, 6 hour/day	No effect on activity level, amount of brain protein or RNA.
York et al. (1982)	Long-Evans rats	Females and offspring	Females exposed to 2100 ppm inhalation during and/or before pregnancy.	No effects on breeding in females or open field or running wheel activity in offspring.
Woolverton & Balster (1981)	CD-1 mice	Male adults	Inhalation of 3,500-7,000 ppm MC	EC50 for inverted screen climbing was about 5,200 ppm.
Moser & Balster (1982)	CD-1 mice	Male adults	Inhalation of 1,000-8,000 ppm MC	Reduced FI response rate beginning at 4,000 ppm.
Larsby et al. (1978)	Rabbit	?	Infusion of MC	Vestibular disturbances beginning at 75 ppm MC in arterial blood.

cardiogram was essentially unaltered; the heart rate was increased and the T-wave was either flattened or inverted. At the point of respiratory arrest, a depressed S-T segment was observed; however, tachycardia was absent.

Herd and co-workers (1973, 1974) confirmed the initial observations of Krantz et al. (1959). They exposed dogs to 10,000 to 40,000 ppm (54,000 to 216,000 mg/m^3) per minute and observed a dose-dependent biphasic decline in arterial blood pressure. Since cardiac output increased initially, the initial decline in pressure (within 10 to 15 seconds after introduction of MC) was due to a decrease in total peripheral resistance (TPR). Injection of phenylephrine (pure alphaagonist) reversed the peripheral vascular effects, indicating that MC does not act directly on the vascular musculature. The second phase of blood pressure decline was found to be associated with a decrease in myocardial contractility, reflected by a decline in both heart rate and stroke volume. Exogenous Ca^{++} reversed the MC induced decline in myocardial contractility, but had no effect on the initial phase of peripheral vasodilation.

Taylor et al. (1976) exposed New Zealand white rabbits to a series of haloalkane chemicals. The animals were first anesthetized with sodium pentobarbital, then fitted with various cannulas allowing for the measurement of mean arterial pressure, left ventricular pressure, left ventricle dP/dt, cardiac output, stroke volume, heart rate, left ventricular end-diastolic pressure, central venous pressure, and peripheral vascular resistance. Table 5-8 lists the left ventricular and hemodynamic effects of 50,000 ppm (270,000 mg/m^3) MC. There was no effect on heart rate, left ventricular end-diastolic pressure, central venous pressure, or peripheral vascular resistance. During exposure, no cardiac arrhythmias were observed nor was there a significant change in pH, oxygen, or carbon dioxide tensions. While this level of exposure would probably be lethal in humans, it is many orders of magnitude greater than levels found in ambient air.

Numerous hydrocarbon compounds have been shown to sensitize the myocardium to catecholamines. In humans, for example, several unexplained deaths have been associated with solvent abuse or overexposure; ventricular fibrillation due to cardiac sensitization has been suggested as the underlying mechanism. The cardiac sensitization potential of MC has been investigated under various circumstances. In an early study, Rennick et al. (1949) reported MC and epinephrine induction of idioventricular rhythms in dogs. Attempts to induce

TABLE 5-8. LEFT VENTRICULAR AND HEMODYNAMIC EFFECTS OF METHYL CHLOROFORM

	Mean Arterial Pressure (mmHg)	Left Ventricular Pressure (mmHg)	Left Ventricle dP/dt (mmHg/sec)	Cardiac Output (ml/min)	Stroke Volume (ml)
Pre-exposure	69±5	97±3	3792±325	423±31	1.47±0.09
1 minute post exposure[a]	45±4	70±5	1433±163	266±26	0.92±0.07

[a] All values at 1 minute exposure are significantly different from pre-exposure values at $p < 0.05$.

Source: Taylor et al. (1976).

MC anesthesia resulted in the sudden death, presumably of cardiac origin, of two animals. Ventricular extrasystoles and ventricular tachycardia were seen in five dogs under barbital anesthesia when epinephrine was injected after "repeated small doses" of MC. Maximum sensitization of the heart to epinephrine occurred after the administration of 0.25 to 0.4 ml/kg of MC. Further administration of this compound produced severe hypotension. Somani and Lum (1965), Lucchesi (1965), and Hermansen (1970) administered MC to dogs or mice as a method for induction of cardiac arrhythmias in studying and characterizing the sensitivity and specificity of adrenergic blocking agents.

Clark and Tinston (1973) evaluated the cardiac sensitizing potencies of 14 halogenated hydrocarbons in conscious beagle dogs. During the last 10 seconds of a 5 min exposure, epinephrine (5 mg/kg) was injected intravenously (bolus). As a control, epinephrine was given prior to exposure and also 10 min after the end of exposure. The electrocardiogram (lead II) was monitored continuously during this procedure. Several dose levels of the chemical being tested were used, each differing by a factor of two. The concentration at which 50% (EC_{50}) of the animals could be sensitized was calculated by a moving average interpolation. The mean concentration of MC which produced cardiac sensitization in 50% of the animals tested was 7,500 ppm (40,500 mg/m^3). The authors found that they could directly predict the EC_{50} for cardiac sensitization by knowing the vapor pressure at 37°C and the partial pressure at the EC_{50}. Table 5-9 lists the EC_{50} for a number of different halogenated hydrocarbons. MC appears to be a highly potent sensitizing agent at near anesthetic levels, with tetrachlorodifluoromethane being the most potent in the series. The authors concluded that cardiac sensitization was probably a structurally nonspecific action and that it was physically toxic.

Reinhardt et al. (1973) investigated five commonly used industrial and household solvents, including MC, to assess their cardiac-sensitization potential. The investigators conducted experiments on unanesthetized, healthy male beagle dogs that had been trained to breathe through a one-way face mask while supported in a standing position by a sling. The dog inhaled house air for 7 minutes and the test compound for 10 minutes. Epinephrine (8 µg/kg in 1 ml of normal saline) was injected i.v. in 9 seconds as a control dose after 2 minutes of breathing air, and as a challenge dose after 5 minutes of breathing the test compound. The 10-minute interval between the two doses was found to be

TABLE 5-9. CONCENTRATION OF CHEMICALS CAUSING CARDIAC SENSITIZATION AND THEIR PHYSICAL PROPERTIES (IN PPM)

Chemical	EC_{50}	Vapor pressure at 37°C (mmHg) P_s	Partial pressure at EC_{50}(mmHg) P_{cs}	Relative saturation for cardiac sensitization P_{cs}/P_s
Tetrachlorodifluoromethane	1,200	99	2	0.02
Carbon tetrachloride	5,000	190	4	0.02
Trichloroethane	7,500	210	6	0.03
Halothane	20,000	480	15	0.03
Trichlorotrifluoroethane	10,000	524	8	0.02
Methylene chloride	24,000	661	18	0.03
Trichlorofluoromethane	12,500	1,186	10	0.01
Dichlorofluoromethane	25,000	2,052	19	0.01
Dichlorotetrafluoroethane	100,000	2,310	76	0.03
Vinyl chloride	50,000	4,218	38	0.01
Propane	200,000	9,538	153	0.02
Bromotrifluoromethane	200,000	15,276	153	0.01
Chlorotrifluoromethane	800,000	40,698	610	0.02

Source: Clark and Tinston (1973).

adequate to prevent additive effects when tested in 13 control dogs subjected to the same procedures, but with air substituted for the test compound. A positive response was considered to be either cessation of cardiac output (ventricular fibrillation) or the development of an arrhythmia that was not observed following the control dose and that was considered to pose a serious threat to life (multiple, consecutive beats of ventricular origin). The concentration of the test compound being delivered to the animal was determined by gas chromatography at 2-minute intervals.

The results obtained for MC indicated no response in 12 dogs at a nominal concentration of 0.25 percent (V/V) and a marked response in 3 of 18 dogs exposed at a nominal concentration of 0.5 percent (V/V); 12 of 12 responded at a nominal concentration of 1.0 percent (V/V). However, unlike the other substances, MC-induced ventricular fibrillation in the animals from the 1.0 percent group reverted to multiple consecutive ventricular beats within a matter of seconds and eventually recovered to a normal cardiac rhythm. The results confirm earlier reports that MC is capable of sensitizing the dog heart to exogenous epinephrine although none of the dogs died.

Trochimowicz and co-workers (1976) were concerned with the problem of haloalkane-induced cardiac sensitization in patients who had survived myocardial infarction. They induced myocardial infarction in beagle dogs and tested for cardiac sensitization to epinephrine after exposure to MC at levels of 2500, 3700, and 5000 ppm (13,500; 19,980; and 27,000 mg/m^3). Myocardial infarction did not significantly alter the threshold for cardiac sensitization. There was no greater potential for cardiac sensitization among dogs having recovered from myocardial infarction as compared to normal healthy animals.

Rabbits have recently been shown, by Carlson (1981), to respond to a combined inhalation exposure to MC and a challenge dose of epinephrine, resulting in spontaneous arrhythmias (premature ventricular contractions). Controls did not exhibit arrhythmias at an exposure level of 5,600 ppm (30,240 mg/m^3) up to 60 minutes, in the absence of a challenge dose of epinephrine. Induction of arrhythmia was examined also by first administering phenobarbital (40 mg/kg) i.p. daily for 4 days prior to exposure or administering microsomal mixed function oxidase inhibitors. Although none of the results reported by Carlson (1981) were statistically significant, both inhibitors appeared to increase the responsiveness of the heart to arrhythmias when compared to controls.

Fifty percent of the rabbits administered SKF-525A (50 mg/kg) 30 minutes prior to exposure exhibited arrhythmias after 7.5 minutes of exposure to MC, following a challenge dose of 2 ug/kg epinephrine. In both inhibitor groups there was a rapid return to normal cardiac rhythm during the recovery period.

Blood analysis revealed trichloroethanol (TCE) as the principal metabolic product. Phenobarbital resulted in an increase in blood TCE but it was not statistically significant. The inhibitors resulted in an increased amount of blood MC. This observation and the tendency of the inhibitor-treated animals to show a higher incidence of arrhythmias led the investigators to conclude that MC, not the metabolites, was responsible for the arrhythmias.

At sufficiently high levels (in the thousands of ppm, for durations of exposure of the order of minutes), MC has been reported to cause significant alterations in cardiovascular function in a variety of experimental animals, including mice, rabbits, dogs, and possibly monkeys. The concentration levels reported for these effects are generally more than an order of magnitude greater than the current TLV for humans of 350 ppm (1,890 mg/m^3) and are likely to be lethal to the experimental animals if the exposure is continued for more than several minutes. Indeed, some experimenters appeared to find it necessary to increase the oxygen content of the inspired gas/air mixture to 40 percent to prevent asphyxia of the exposed animals. That they appeared unable to find effects at lower exposure levels is noteworthy. Also noteworthy is the fact that many of the investigators reported complete recovery of the animals if the exposure was stopped. This was the case, for example, with the dog experiments of Reinhardt et al. (1973), and Trochimowicz et al. (1976). At necropsy following sacrifice of several of the animals several months after exposure, there was no pathology attributable to the exposure _per se_. Delayed cardiotoxicity from acute exposure has not been demonstrated.

5.2.4 Dermal Effects

MC was one of seven solvents tested for dermal effects by Kronevi et al. (1981). Guinea pigs (17) were anesthetized with pentobarbital, i.p., and one ml of an inhibited formulation of MC was applied to an area (3.1 cm^2) on the clipped back skin, through a hole in the cover glass. The hole was closed with a small piece of glass glued with α-cyanoacrylate. At 15 minutes, 1.4, and 16 hours, glass rings were removed and whole skin specimens from exposed sites were excised and fixed in 10% formalin. Samples from adjacent non-exposed sites were taken as controls.

Pyknotic nuclei were seen in all layers of epidermis, beginning with the 15 minute sample. It was reported that degeneration of nuclei progressed in proportion to increased exposure times involving pyknosis and karyolsis. A marked intercellular edema was observed after 15 minutes; edema was hardly recognizable at 1 hour and not at all after 4 and 16 hours; at this time, it was totally replaced by junctional separation. A slight, diffuse pseudo-eosinophilic infiltration appeared in the upper part of the dermis after 4 hours and became severe after 16 hours.

Karyopyknosis was a finding common to all the solvents evaluated. Karyolysis, intercellular edema and junctional separation was common to most of the solvents.

The results of this one study suggest that skin contact with MC be minimized.

5.3 TERATOGENICITY, MUTAGENICITY, AND CARCINOGENICITY

It has been proposed that the susceptibility of individuals to cancer is related to their ability to metabolize carcinogenic compounds to benign molecules and, conversely, to their capacity to metabolize benign compounds to carcinogens (Kellerman et al., 1973). Susceptibility may be partly explained by genetic differences involving enzymatic pathways, repair mechanisms, and immune response mechanisms. An assessment of the carcinogenic potential of MC must therefore take into account tissue concentrations of MC during typical exposures (e.g., TWA, 350 ppm), as well as the extent and nature of MC metabolism. Both these aspects have been extensively reviewed in Chapter 4. While our knowledge is still limited in these areas, it can be concluded that MC is metabolized in humans to a very small extent. About 6 percent or less of the body dose is converted to trichloroethanol and trichloroacetic acid. The mechanism of this overall reaction is unknown. The available studies on carcinogenicity and tetratogenicity are summarized in Table 5-10.

5.3.1 Teratogenicity, Embryotoxicity, and Reproductive Effects

5.3.1.1 Overview--This review subscribes to the basic viewpoints and definitions of the terms "teratogenic" and "fetotoxic" as summarized and stated by Chernoff (1980):

> Generally, the term "teratogenic" is defined as the tendency to produce physical and/or functional defects in offspring in utero. The term "fetotoxic" has traditionally been used to describe a wide variety of embryonic and/or fetal divergences from the normal which cannot be classified as gross terata (birth defects) -- or which are of unknown or doubtful significance. Types of effects which fall under the very broad category of fetotoxic effects are death, reductions in fetal weight, enlarged renal pelvis edema, and increased incidence of supernumary ribs. It should be emphasized, however, that the

TABLE 5-10. ONCOGENIC AND TERATOGENIC TESTING OF METHYL CHLOROFORM

Test System	Species	Reference	Results
Teratogenicity			
Organogenesis	Chick embryo	Elovaara et al., 1979	Positive; high toxic dose, skeletal abnormalities
Mammalian gestation	Mice (drinking water)	Lane et al., 1982	Negative
Mammalian gestation	S/D rat, S-W mice (inhalation)	Schwetz et al., 1975	Negative
Mammalian getstation	L-E rat (inhalation)	York et al., 1982	Slight but possible reversible delay in development
Carcinogenicity			
NCI bioassay - 2 yr	Osborne-mendel rats, and $B_6C_3F_1$ mice and oral gavage; 750 and 1500 mg/kg (rat)	NCI, 1977; NCI Clearinghouse on Environmental Carcinogens, 1977	Inconclusive; high animal mortality
NTP bioassay - 2 yr	Rat and mouse gavage		Study completed. Peer review of results scheduled for January 1983.
Industry bioassay - 1.5 yr	S/D rats, inhalation 875 and 1750 ppm		Negative

NOTE: See appendix for discussion of chemical purity.

phenomena of terata and fetal toxicity as currently defined are not separable into precise categories. Rather, the spectrum of adverse embryonic/fetal effects is continuous, and all deviations from the normal must be considered as examples of developmental toxicity. Gross morphological terata represent but one aspect of this spectrum, and while the significance of such structural changes is more readily evaluated, such effects are not necessarily more serious than certain effects which are ordinarily classified as fetotoxic--fetal death being the most obvious example.

In view of the spectrum of effects at issue, the Agency suggests that it might be useful to consider developmental toxicity in terms of three basic subcategories. The first subcategory would be embryo or fetal lethality. This is, of course, an irreversible effect and may occur with or without the occurrence of gross terata. The second subcategory would be teratogenesis and would encompass those changes (structural and/or functional) which are induced prenatally, and which are irreversible. Teratogenesis includes structural defects apparent in the fetus, functional deficits which may become apparent only after birth, and any other long-term effects (such as carcinogenicity) which are attributable to in utero exposure. The third category would be embryo or fetal toxicity as comprised of those effects which are potentially reversible. This subcategory would therefore include such effects as weight reductions, reduction in the degree of skeletal ossification, and delays in organ maturation.

Two major problems with a definitional scheme of this nature must be pointed out, however. The first is that the reversibility of any phenomenon is extremely difficult to prove. An organ such as the kidney, for example, may be delayed in development and then appear to "catch up". Unless a series of specific kidney function tests are performed on the neonate, however, no conclusion may be drawn concerning permanent organ function changes. This same uncertainty as to possible long-lasting after effects from developmental deviations is true for all examples of fetotoxicity. The second problem is that the reversible nature of an embryonic/fetal effect is one species might, under a given agent, react in another species in a more serious and irreversible manner.

It is not possible, on the basis of limited available data, to define the full potential of MC to produce adverse teratogenic or reproductive effects. Human epidemiology studies have not been conducted to evaluate the effects of MC on the exposed population. Each of the available mammalian studies had methodological drawbacks that do not allow for conclusive evaluation of the ability of MC to produce a teratogenic response over a wide range of doses, which should include doses high enough to produce signs of maternal toxicity and lower doses which do not produce this effect. Some of the teratology studies used rats and mice and only single doses of MC which produced signs of maternal toxicity. Other studies in chicken embryos have indicated that MC disrupts embryogenesis in a dose-related manner. However, since administration of MC directly into the air space of chicken embryo is not comparable to administration of a dose to animals with a placenta, it is not possible to interpret this result in relationship to the potential of MC to cause adverse human reproductive effects.

In summary, although several studies have been conducted to evaluate the ability of MC to cause adverse teratogenic, embryotoxic and reproductive effects, the limitations of the available data do not allow for a full assessment of these effects. A better assessment of these effects could be performed if the available studies met criteria similar to those suggested for teratogenicity and reproductive testing (U.S. EPA, 1978).

5.3.1.2 Human Studies--No clinical reports associate maternal exposure to methyl chloroform with congenital malformations in offspring. No epidemiological studies have been performed.

5.3.1.3 Animal Studies--All studies performed to date in mammals have been done in rats and mice. On the basis of these studies, it does not appear that short- or long-term exposure to MC results in teratogenic effects in rats or mice. Delays in fetal development have been observed in both species, but this may be a reversible effect. It should be noted, however, that most of these studies evaluated only one dosage level per animal species, which included dosages twice the maximum excursion limit for short-term exposures of rats and mice and six times the maximum excursion limit for long-term exposures of rats. Another study in chicken embryos indicates that MC may have teratogenic potential in this species. However, since it is not known how comparative studies in chicken embryos are to those in other mammalian species, the teratogenic potential of MC in chickens cannot be related to other animals without additional data. In addition, no multigenerational studies of mammalian reproductive performance have been performed under conditions of inhalation exposure.

5.3.1.3.1 Rats--Schwetz et al. (1975) report results from Sprague-Dawley rats exposed via inhalation to 875 ppm (4,725 mg/m^3) of MC for 7 hours daily on days 6 through 15 of gestation (Day 0 = the day sperm were observed in smears of vaginal contents). Control rats were exposed to filtered air. Dams were evaluated for body weight gain, food consumption and various organ weights. Maternal carboxyhemoglobin level determinations were performed on blood samples collected via orbital sinus puncture immediately following the third and tenth (last) exposure. One-half of the fetuses in each litter were examined for soft-tissue malformations (free-hand sectioning), and one-half were stained and examined for skeletal malformations. One fetus in each litter was randomly selected and evaluated using histological techniques following serial sectioning.

Twenty-three litters from dams exposed to 875 ppm (4,725 mg/m^3) of methyl chloroform were evaluated. No effect was observed on maternal body weight or food consumption. The mean absolute liver weight was increased as compared with control, however the mean relative liver weight was unchanged. No embryotoxic or teratogenic effects were observed which were attributable to maternal MC exposure.

York et al. (1982) exposed female Long-Evans rats by inhalation to dosages of 2100 ± 200 ppm (11,340 ± 1,080 mg/m^3) MC for 6 hours daily, 5 days per week, in the following regime: (1) two weeks prior to mating through day 20 of gestation; (2) two weeks prior to mating only; (3) throughout gestation only; (4) controls which were exposed to filtered air before and during pregnancy. Day 1 of pregnancy was designated as the day spermatozoa were observed in smears of vaginal contents. One-half of each group was sacrificed on day 21 and assessed for signs of maternal toxicity, embryotoxicity or teratogenicity. The other one-half were allowed to deliver young naturally and the young were later evaluated for behavioral alterations and for observation of gross lesions. When possible, litters were culled to four pups of each sex on day 4 post-parturition and to two pups of each sex at 21 days postpartum. Pups were evaluated for behavioral effects (see 5.2.2) and carcinogenicity. Surviving rats were sacrificed and necropsied at 12 months of age.

York et al. (1982) reported that both total fetal body weight and male fetal body weight were significantly depressed in litters when dams were exposed during pregnancy. Delayed ossification was more frequent in fetuses which had been exposed before and during pregnancy, and a delay in the development of the kidney was a more frequent observation in fetuses in all exposed groups. These effects are thought to be indicative of a slight, but possibly reversible delay in development. No treatment-related behavioral effects were observed in the pups, nor were significant signs of maternal toxicity observed.

5.3.1.3.2 Mice--Schwetz et al. (1975) exposed Swiss-Webster mice to 875 ppm (4,725 mg/m^3) of MC, twice the maximum excursion limit, for 7 hours daily, on days 6 through 15 of gestation (day 0 = day a vaginal plug was observed).

Dams were Caesarean sectioned on day 18 of gestation and thirteen litters were evaluated. Methodology similar to that described previously (Schwetz et al. 1979) in rats was used, with the exception that food consumption was not monitored.

Mean and relative maternal liver weights in the exposed mice were slightly but not statistically decreased. Also, fetuses from the exposed group were slightly but not statistically smaller (both the crown-rump length and the body weight). This type of observation is thought to indicate a slight, but perhaps reversible delay in fetal development. No increased soft tissue or skeletal variations of the fetuses were attributable to maternal exposure to MC.

Lane et al. (1982) investigated the effects of MC on the reproductive capability of mice using a multigenerational reproductive protocol modified to include screening for teratogenic and dominant lethal effects. Animals were exposed to TCE for 35 days, then 10 male and 30 female mice (parental generation F/0) were mated to produce the first set of offspring (FIA). After the F/1A were weaned, the F/0 adults were remated to produce the second set of offspring (F/1B). A parental stock was chosen from the F/1B litter (30 females, 10 males) to produce a second generation of offspring (F/2A). After weaning the F/2A, the F/1B adults were remated to produce offspring (F/2B) for use in teratology and dominant lethal screening tests.

The MC (Aldrich Chemical Co. 95% pure with 3% dioxane) was dissolved in a solution of Emulphor EL-620 (GAF Corp. Kinden, New Jersey) (1% Emulphor dissolved in deionized water) then further diluted with deionized water to concentrations of 0.58, 1.75, and 5.83 mg/ml or a nominal dose of approximately 100, 300, and 1000 mg/kg/day (assuming a 35 g mouse consumes 6 ml/day). The test animals were continuously maintained on MC solutions or control solution (deionized water, or water containing 0.17 mg/ml p-dioxane dissolved in 1.0% Emulphor solution). Fresh drinking solutions were prepared twice weekly and placed in amber glass bottles with cork stoppers and stainless steel drinking tubes. The authors reported no decreases in the amount of fluid consumed in either MC or the solvent control groups.

In this study MC produced no treatment related signs of toxicity such as lowered body weights or gross pathological changes in major organs. There were no significant differences in the fertility index or gestation index observed in the F/1A, F/1B, or F/2A generations. There were sporadic incidences of increased mortality throughout the generations but these were not dose-related. There was no difference in the litter sizes at birth, pup body weights, survival of pups at days 4 and 21 of birth. There was a decrease in the survival indices for the F/2A generation as compared to values for the F/1A and F/B generation but these decreases were not dose related. In addition, in the dominant lethal screening there were statistically significant differences; however, both increases as well as decreases were observed in the ratio of dead to live fetuses. In the teratology screening, the continuous administration of MC produced no apparent adverse reproductive effects, no visceral or skeletal abnormalities; however, it should be noted that continuous administration is not a routine protocol for evaluating teratogenic effects. In the lowest dosage groups, none of the females had copulating plugs which made it impossible to time the pregnancies; therefore, no teratological examinations were performed. The reason for this effect was not disclosed in the paper.

In conclusion, this study is inadequate from the standpoint of determining whether MC has the potential to cause adverse reproductive or teratogenic effects because animals were not given doses high enough to produce overt signs of toxicity. Another confounding factor is that a determination of the amount of MC that may have partitioned into the head space of the inverted drinking solution bottles was not made (Lane, personal communication, 1982). Thus, it is not clear how much MC each animal received between solution changes. It had been determined, however, that MC was stable in solution, based upon measurements of stored drinking solutions. It appears that under the conditions of the experiment, mice (Swiss ICR) administered MC in drinking water (nominal doses of 100, 300, and 1000 mg/kg/day) did not exhibit any observable adverse reproductive effects.

5.3.1.3.3 Chicken embryos--Elovaara et al. (1979) evaluated the effects of a number of aliphatic hydrocarbons on the development of chick embryos and reported the toxicity and teratogenic potential of MC in relationship to those of other aliphatic chlorinated hydrocarbons. MC was injected into the air space of fertilized chicken eggs at 2, 3, and 6 days of incubation and the rate of survival or death after 14 days of incubation was used as a measure of embryotoxicity. The approximate LD_{50} value of MC varied between 50 and 100 µM/egg, depending upon time of injection. The types of abnormalities reported

TABLE 5-11. MUTAGENICITY TESTING OF METHYL CHLOROFORM IN BACTERIA

Reference	Test System	Strain	Activation System	Concentration		Result	Comment
				Formulation	%		
Litton 1975	Salmonella/S9: spot test and suspension test	TA 1535 TA 1537 TA 1538	PCB induced liver, lung and testes S9 mix from adult male animals: ICR random bred mice, Sprague-Dawley rats and Macaca mulatta monkeys.	99+	5.0 2.5	99+% formulation reported positive with TA 1535 both with and without metabolic activation. Result was reported to be repeatable. The other formulations were reported to be negative.	1. All formulations reported to be not soluble at test concentrations. 2. Toxicity reported to be variable (In half of the tests, as many or more survivors were observed at the high dose compared to the low dose). 3. Strains TA 98 and TA 100 not tested (not available at time test conducted). 4. No information about the identity of the stabilizers and other components. 5. No special precaution taken to prevent evaporation of the compound, but test reported to be conducted in suspension.
				96	2.0 1.0		
				95.65	1.0 0.5		
				93.75	0.5 0.25		
Henschler et al. 1977	Salmonella/S9	TA 100	PCB induced rat liver S9 mix.	Not reported.		Reported negative.	1. No precautions taken to prevent evaporation reported. 2. No data presented, therefore, cannot evaluate. 3. Only one strain tested.

TABLE 5-11. (Continued)

Reference	Test System	Strain	Activation System	Concentration	Result	Comment
Simmon et al. 1977	Salmonella/S9: conducted in sealed desiccator	TA 1535 TA 1537 TA 1538 TA 98 TA 100	PCB induced rat liver S9 mix.	(Extrapolated from figure 21) 0, 100, 200, 300, 400, 500, 750 1000 µl/9-liter desiccator.	TA 100 Dose +S9 -S9 0 125 125 100 130 145 200 125 180 300 17 185 400 200 - 500 200 220 750 260 210 1000 280 225	1. Results indicate ability of methyl chloroform to mutate bacteria with and without metabolic activation when precautions are taken to ensure exposure of test organisms. 2. Data were presented for TA 100 only. 3. Exact purity of test compound not given, but reported to be high.
Taylor 1977	Salmonella/S9: plate incorporation tests	TA 1535 TA 1537 TA 98 TA 100	Aroclor-activated rat liver S9 mix. Different amounts tested (0, 10, 20, 30, 40, and 50 µl/plate).	0, 50, 100, 200, 300, and 500 µl/plate	Reported negative.	1. No precautions reported to have been taken to prevent evaporation of the test material. 2. Protocol not adequately described. 3. No concurrent positive controls reported. 4. The purity of the test chemical not reported.

TABLE 5-11. (Continued)

Reference	Test System	Strain	Activation System	Concentration	Result		Comment
Snow et al. 1979	Salmonella/S9: conducted in sealed chambers	TA 100	Methyl chloroform induced Syrian golden hamster liver S9 mix.		Aldrich Sample	PPG Sample	1. Only one strain tested. 2. Results indicate ability of methyl chloroform to mutate bacteria with or without metabolic activation when precautions are taken to ensure exposure of test organisms. The response is somewhat better with S9 mix. 3. Linear dose responses obtained with no significant differences found between Aldrich or PPG samples at any concentration tested. 4. Protocol not completely described. 5. Purity of Aldrich sample not reported. Purity of the PPG sample reported to be high but information about composition not provided.
					(without activation)		
				0[*]	144,115,130	144,115,150	
				500	234,251,235	225,232,233	
				750	271,271,274	263,301,262	
				750	271,271,274	263,301,262	
				1000	315,270,310	307,283,268	
				1500	355,336,340	398,360,336	
					(with activation)		
				0	122,143,119	122,143,119	
				500	324,281,312	266,291,297	
				750	365,346,351	359,333,348	
				1000	384,402,393	373,372,407	
				1500	485,432,430	471,467,430	
Nestmann et al. 1980	Salmonella/S9 conducted in sealed desiccators	TA 98 TA 100 TA 1535	PCB induced rat liver S9 mix	ml/desiccator 0.1 0.5 1.0	Mutagenic in TA100, up to 2.5-fold increase, and TA1535, up to 6-fold increase.		1. Purity of test sample unknown. 2. Experimental values not given.

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[*] µl/5.6-liter Billups-Rothenberg Modular IncubatorChamber

TABLE 5-11. (Continued)

Reference	Test System	Strain	Activation System	Concentration	Result	Comment
Gocke et al. 1981	Salmonella/ S9 conducted in sealed desiccator	TA 1535 TA 1537 TA 1538 TA 98 TA 100	PCB induced rat liver S9 mix	ml/desiccator 0.5 1.0 1.5 2.0	Dose-related fourfold increase in TA 1535.	1. Purity not given but reported to have correct elementary analysis and melting point.
Miyata et al. 1981	Salmonella/ preincubation assay	TA 1535 TA 1537 TA 92 TA 94 TA 98 TA 100	PCB induced rat liver S9 mix	ml/plate 30 100 300 1000 3000	Negative. Toxicity observed at two highest doses.	1. Protocol precludes comparison with studies employing airtight chambers.

were absence of eye(s), upper beak deformations, exencephaly, brain hemorrhages, paleness (anemia), profound edemas either in the rump sacs or other areas, defects in external viscera and musculoskeletal defects of lower extremities. The spontaneous background level of malformations in vehicle-injected controls included only eye and skeletal abnormalities. This study indicates that MC has possible teratogenic potential when evaluated in chicken embryos, and that additional experiments should be performed for further evaluation. A scientific basis for the comparison of developmental toxic effects in various animal species is needed before results in chickens can be compared with other mammalian animal species.

5.3.2 Mutagenicity

5.3.2.1 Gene Mutations In Bacteria--A number of reports have been prepared about the mutagenicity of MC in bacteria; all were conducted using the *Salmonella*/S9 system (Table 5-11). Two of the reports, Henschler et al. (1977) and Taylor (1977), were reported to be negative. In the report by Henschler no data are presented. In the unpublished report by Taylor no concurrent positive controls were reported. Thus, these reports cannot be adequately evaluated.

Because of methyl chloroform's volatility and low solubility in water, special precautions need to be taken to ensure adequate exposure of test organisms. No such precautions were taken in the tests conducted by Litton Bionetics (1975) for Dow Chemical Company. In this study various formulations of MC (i.e. 99+%, 96%, 95.65%, and 93.75%) were assayed for mutagenic potential in *Salmonella* strains TA 1535, TA 1537, and TA 1538, both with and without metabolic activation (S9 mix prepared from tissue of PCB-induced mice, rats, and monkeys). No information was provided concerning the stabilizers for other components present in the formulated samples tested. Preliminary toxicity testing was conducted to determine the appropriate test doses. The test doses used were different for each formulation and are presented in Table 5-11. It was reported by the contractor that the chemicals tested were not soluble in the aqueous testing environment, and it was stated, for the 99+% formulation at least, that "the toxicity from test to test was quite variable depending upon the ability to effectively disperse the compound in the testing medium." The low solubility of MC coupled with its high volatility raise the concern that, in the tests conducted by Litton Bionetics, exposure of the test organisms may have been minimal. *Salmonella* tester strain TA1535 was reported to exhibit a reproducible mutagenic response to the 99+% formulation, but it is stated in the report that "the mutagenicity of this chemical for indicator strain TA1535 must be considered presumptive for the following reasons:

A. The positive response is only evident at high dose levels which generally result in low population survivals (high toxicity). Thus one cannot exclude some type of selection.

B. The data from activation plate tests does (sic) not indicate any activity. The activation plate tests were repeated and were negative in those tests as well."

With respect to point A, an examination of the computer print-outs summarizing the mutagenicity of MC for strain TA1535 both with and without activation reveals that the population of cells in the high dose group was equal to or greater than the cells in the low dose group in two out of four cases, including the experiment in which the highest mutation frequency was observed. In other words, there does not seem to be significant cytotoxicity at the high dose level which could possibly result in a spurious positive result.

With respect to point B, the plate activation tests performed in this experiment were spot tests. The proper conduct of a bacterial spot test requires that the compound be soluble in water, dissolving through the agar from point of placement outward, forming a concentration gradient. Since MC is volatile and was not soluble in the testing performed by Litton-Bionetics, the negative results of the plate tests cannot be considered evidence supportive of the nonmutagenicity of MC in bacteria: therefore, the study by Litton-Bionetics (1975) is considered to be an inadequate assessment of the mutagenicity of MC.

Four tests of the mutagenic potential of MC in bacteria were conducted using protocols designed to prevent excessive evaporation of this substance and thereby ensure exposure of the indicator organisms. All reported positive results in tester strains TA100 and/or TA1535 (Simmon et al., 1977; Snow et al., 1979; Nestmann et al., 1980; and Gocke et al., 1981). The testing performed by Simmon and co-workers was conducted using the standard battery of *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100, both with and without PCB-induced rat liver S9 mix for metabolic activation. The concentrations used for testing (extrapolated from figure 21 in the paper) were 0, 100, 200, 300, 400, 500, 750, and 1000 µl/9-liter desiccator. A weak dose-related response was observed for TA100 both with and without metabolic activation.

These results indicate that commercially available MC does possess mutagenic activity in Salmonella. The purity of the MC sample (obtained from Aldrich Chemicals) tested was not given; however, it may have contained mutagenic contaminants (see discussion by Henschler et al. 1980). Subsequently, a Matheson, Coleman, and Bell sample (MCB) was obtained by Simmon and colleagues. This sample was analyzed (Dr. Ronald Sponggord, SRI International, personal communication, 1982) and found to be 84% pure and to contain several identifiable contaminants (i.e., p-dioxane, 1,1-dichloroethylene, nitromethane, 1,1-dichloroethane, chloroform, and trichloroethylene and 1,2-epoxybutane, reported mutagens). After distillation to increase the purity to 98% and acid hydrolysis to remove the 1,2-epoxybutane contaminant the material was reanalyzed and also tested for mutagenicity. The MCB samples showed nearly the same mutagenic responses before and after purification (Dr. Kristien Mortelmans, SRI International, personal communication, 1982). However, 1-2% unidentified impurities were also detected in the "purified" MCB sample. Thus, it is not possible to unequivocally ascribe the mutagenic activity of this sample to MC.

In their studies, Snow et al. (1979) tested two samples of MC in Salmonella strain TA100 both with and without metabolic activation. Testing conducted with metabolic activation employed an S9 mix obtained from MC-induced Syrian golden hamster livers. Similar to the study performed by Simmon et al. (1977), precautions were reported to have been taken to prevent evaporation of MC. Doses of 0, 500, 750, 1000, and 1500 µl/5.6 liter Billups-Rothenberg Modular Incubator Chamber were employed, and nearly identical linear dose-responses were observed for TA100 (see result column, Table 5-12) in the two samples of MC tested. One of the samples was from Aldrich (97% MC stabilized with 3% p-dioxane) and the other was from PPG Industries (also estimated to be 97% pure). These samples were analyzed by mass spectrometry. In addition to MC, the Aldrich sample was found to contain dioxane, 1,1- or 1,2-dichloroethylene, nitromethane, trichloroethylene, methylisobutyl ketone, 1,1,2-trichloroethane, and toluene. Acetone, nitromethane, methyl ethyl ketone, dimethyl formamide, toluene, trichloroethylene, and 1,1- or 1,2-dichloroethylene were identified as contaminants in the PPG sample. Of the impurities detected, only 1,2-dichloroethylene (vinylidene chloride) and trihloroethylene have been reported in the literature to be mutagenic. These were only minor components; however, most of the impurities were accounted for by acetone, methyl ethylketone, toluene, and dioxane. Even if one were to assume that the 3% impurities present were accounted for exclusively by vinylidene chloride or trichloroethylene, it is not likely that the mutagenic response can be accounted for by these substances. Both require the presence of an exogenously supplied metabolic activation system to yield a positive response in bacteria, yet linear dose related positive responses were obtained for both samples in testing conducted without metabolic activation.

Nestmann et al. (1980) used Salmonella strains TA98, TA100, and TA1535 both with and without PCB-induced rat liver S9 mix for metabolic activation in their testing of MC. 100, 500, and 1000 µl aliquots (Fisher Scientific: purity not given) were placed in open glass dishes inside a dessicator. The plates were exposed to MC vapors for 16 hours and incubated for a total of 72 hours before scoring. The authors report that under the conditions of test, MC was not detected as mutagenic by strain TA98 but induced up to a 2.5-fold increase in revertants in strain TA100 and up to a 6.5-fold increase in revertants in strain TA1535. The authors' conclusions cannot be independently assessed because the experimental values were not given.

Gocke et al. (1981) used Salmonella strains TA100 and TA1535 both with and without PCB-induced rat liver S9 mix for metabolic activation to assess the mutagenic potential of MC. Aliquots of 500, 1000, 1500, and 2000 µl (values extrapolated from Figure in reference) were placed in airtight desiccators and the bacteria were exposed for 8 hours. After incubation and scoring, there was about a 1.3-fold increase noted in revertants for TA100 (i.e. 150 compared to 200 revertants at 0 and 200 µl MC, respectively) and about a 10-fold increase in revertants for TA1535 (i.e. 20 compared to 200 revertants at 0 and 2000 µl MC, respectively).

The results of Snow et al. (1979), Nestmann et al. (1980), and Gocke et al. (1981) strengthen the observations by Simmon et al. (1977) that MC is a weak mutagen in Salmonella when exposure occurs in airtight chambers. The nearly identical responses achieved after testing these samples of MC obtained from different sources support the conclusion that MC is a weak mutagen causing primarily base-pair substitution mutations.

When MC was tested for mutagenicity using a liquid suspension preincubation procedure to prevent its evaporation and to insure exposure to the Salmonella test strain bacteria (i.e., TA1535, TA100, TA92, TA1537, TA98, and TA94) a negative response was obtained (Miyata et al., 1981). The testing was conducted both with and without PCB-induced rat liver microsome S9 mix for metabolic activation. Five concentrations of MC from 30 to 3000 µl/plate were employed. Toxicity was observed at the two highest dose levels, but no increase in revertant counts was observed. It is difficult to compare the results from Miyata et al. (1981) with those from investigators who exposed Salmonella to MC in desiccators because of differences in testing protocols. The difference in response may be due to a number of factors, including the length of time the organisms were exposed to MC under special treatment conditions.

5.3.2.2 Genotoxicity In Eukaryotes--In addition to testing MC in Salmonella, Gocke et al. (1981) used the Drosophila sex-linked recessive lethal test. A 25 mM solution of MC in 5% saccarose was fed to wild-type Berlin K Male flies for an unreported period of time. These males were then mated to Basc females (25 mM reportedly close to the LD_{50}). Three broods were scored (i.e., mated to fresh virgin females for 3, 3, and 4 days after exposure, respectively). Two lethals out of 1226 flies were observed in the first brood. The values for broods 2 and 3 were 0/557 and 0/76 respectively. These values do not demonstrate an increased incidence in sex-linked recessive lethals. However, the experiment is judged to be an inadequate test because the small number of chromosomes scored would preclude the detection of a moderate or weak mutagen. At least 7000 chromosomes in both the control and treated groups are required to be scored in order to make the determination that exposure to a chemical substance does not increase the mutation frequency twofold (Lee et al., in press). In addition, the concern is raised in the testing by Gocke et al. (1981) that the actual amount of MC ingested by the exposed males was less than predicted due to the volatility of the substance.

Tests of MC for mutagenicity and recombinogenicity in yeast have been conducted by two laboratories (Litton Bionetics 1975 and Loprieno et al. 1979). Both reported negative results (Table 5-14). The Litton Bionetics study was conducted at the same time as was the testing of MC in bacteria discussed in the previous section, and many of the deficiencies noted above concerning the bacterial tests apply to the tests with yeast as well. No special precautions were reported to have been taken to prevent evaporation of the test compound; the compound was not soluble under the condition of test, and the toxicity results were reported to be variable. In half the cases as

TABLE 5-12. MUTAGENICITY TESTING OF METHYL CHLOROFORM IN DROSOPHILA

Reference	Test System	Genetic Cross	Dose	Results			Comment
				I	Brood II	III	
Gocke et al. 1981	Sex-linked recessive lethals	$\frac{\text{Basc}}{\text{Basc}}$ x Berlin K	25 mm in 5% saccharose	$^{2}/1226$	$^{0}/557$	$^{0}/76$	1. Small sample size precludes detection of moderate and weak mutagens. At least 7000 chromosomes should be scored. 2. MC may have evaporated from saccharose solution. 3. Broods correspond to 3, 3 and 4 days post treatment, respectively.

TABLE 5-13. MUTAGENICITY TESTING OF METHYL CHLOROFORM IN YEAST

Reference	Test System	Strain	Activation System	Concentration		Result	Comment
				Formulation	%		
Litton 1975	Saccharomyces Cerevisiae: gene conversion mix.	D4	PCB induced Sprague-Dawley rat liver S9 2.25	99+	4.5	Reported negative. trations employed.	1. Concentrations reported to be not soluble at the test concen-
				96	2.0 1.0		2. Toxicity reported to be variable (in many cases as many or more survivors observed at the high dose as at the low dose).
				95.65	2.0 1.0		3. No information about stabilizers or other chemical substances in the formulations.
				93.75	5.0 2.5		4. No special precautions taken to prevent evaporation of methyl chloroform but tests reported to be conducted in suspension.
Loprieno et al. 1979	Schizosaccharomyces pombe forward mutation	ade 6-60/ rad 10-198/ h-	Host mediated assay B6C3F1 mice.	0 or 5000 mg/kg administered by gavage to mice. yeast exposed for 3, 6, or 16 h.		Reported negative.	1. Preliminary results; protocol not fully presented. 2. MTD may not have been employed. 3. Unclear if negative and positive controls performed . concurrently. 4. Unclear if test compound was absorbed from GI tract and exposed test organisms. 5. No in vitro testing performed. 6. Insufficient sample size screened.

many or more survivors were observed at the high dose as were observed at the low dose. Like the bacterial studies, Litton Bionetics' testing of MC to induce gene conversion in Saccharomyces cerevisiae is judged to be inadequate. The volatility and insolubility of MC and the absence of clear cut, reproducible toxicity raise the likelihood that the cells were not adequately exposed.

Based on preliminary testing in the host-mediated assay in B6C3F1 hybrid mice, Loprieno et al. (1979) have reported that MC administered by gavage at 500 mg/kg did not increase the incidence of forward mutations in Schizosaccaromyces pombe measured after treatment times of 3, 6, and 16 hours. No information was provided concerning the ability of MC to be absorbed and transported to the peritoneum, thereby adequately exposing the yeast cells, and no information is provided concerning whether or not testing was conducted to determine the ability of MC to induce mutations in vitro. Furthermore, no data are presented concerning a determination of the toxicity of the substance to mice after acute exposure to arrive at a maximum tolerated dose for conducting the host-mediated assay. Besides the concerns that the indicator organisms may not have been adequately exposed to MC, the report does not provide adequate information concerning the design and conduct of the testing, and this in turn makes it impossible to assess the significance of the results. (Procedures used to measure mutagenicity are not specified and it is not clear if concurrent positive and negative controls were performed.) The most important consideration in an analysis of this test is that less than 400,000 colonies were scored for mutagenicity. In this forward mutation assay, which is based on the detection of altered colony color, no selection is used. Therefore, only a small sample size is scored and this precludes the detection of weak mutagens.

Two studies have been published on the ability of MC to cause chromosome aberrations (Table 5-14). In the test by Quast et al. (1978) Sprague-Dawley rats were exposed to 0, 875, and 1750 ppm MC 6 hours/day, 5 days/week for 52 weeks. The highest dose is about 1/8 the LC_{50} 7 h exposure. Three males and three females/group were sacrificed and bone marrow cells analyzed for aberrations. Fifty cells per male but much fewer than 50 cells per female were scored. Although no increased incidence of aberrations were observed, the small number of cells analyzed and the lack of a concurrent positive control lead us to judge this study as inadequate.

TABLE 5-14. MUTAGENICITY TESTING OF METHYL CHLOROFORM: MAMMALIAN *IN VIVO* CYTOGENETICS TEST

Reference	Test System	Strain	Activation System	Concentration		Result		Comments
Quast et al. 1978	Chromosome aberrations in rat marrow cells	Sprague-Dawley, spartan substrain	Sex	ppm	# Cells	# Aberrations		1. Inhalation 5 days/week, 6 h/day for one year. 2. Number of cells scored insufficient for adequate interpretation of the results. 3. Treatment had no effect on body weight of rats. MTD may not have been employed. Dose used is about 1/8 acute LD_{50}.
			Males	0	149	0		
				875	150	0		
				1750	150	0		
			Females	0	105	0		
				875	65	1*		
				1750	38	0		
Gocke et al. 1981	Micronuclei	NMRI		Two i.p. injections (one each at 0 and 24 h of 0, 266, 1000, and 2000 mg/kg)		Dose	%Micronuclei	1. Spontaneous control level is low compared to other control levels reported in paper (i.e. about 2%). Apparent twofold increase in micronucleus formation judged to be suggestive but not demonstrating positive response.
						0	1.3	
						266	2.0	
						1000	3.0	
						2000	2.9	

*Chromatid aberration from one animal from which 15 cells are analyzed.

Gocke et al. (1981) assessed the ability of MC (Merck, Darmstadt: purity not given) to cause micronuclei in polychromatic erythrocytes (PCEs). Two male and two female NMRI mice were used for each of 3 dose levels of MC, (266, 1000, and 2000 mg/kg). The highest dose approximates the LD_{50} for mice. Two intraperitoneal injections of each dose were given, one each at 0 and 24 hours, and the animals sacrificed at 30 hours, the bone marrow removed and marrow smears made and scored for the presence of micronuclei in PCE. An apparent dose-related response was observed. The treated controls had 1.3% micronuclei compared to 2.9% in the animals receiving 2 injections of 2000 mg/kg. This represents a two-fold increase in micronucleus formation. However, the control value was low compared to the other controls reported in the paper (about 2% PCEs with micronuclei). Thus, the response is considered to be suggestive but not demonstrative of a positive effect.

A collaborative study entitled the International Program for the Evaluation of Short-Term Tests for Carcinogenicity (IPESTTC) (de Serres and Ashby 1981) was sponsored by Imperial Chemical Industries and the Medical Research Council in the United Kingdom and the National Institute of Environmental Health Sciences in the U.S.A. to assess the ability of short-term tests to predict carcinogenicity. Forty-two coded chemical substances of high purity including MC were tested in 23 different assays (e.g., gene mutation tests in bacteria, yeast, and mammalian cells in culture; SCE formation in vitro and in vivo; chromosome aberrations in vitro, etc.) and some assays were conducted in more than one laboratory. Although a battery of tests were conducted in this study, they are not judged to provide an adequate assessment of the mutagenicity of MC. The intent of the program was to determine how well standard assays compared when testing coded samples. Many of the chemical substances selected for testing were chosen because of problems detecting them in short-term assays. Small samples of the test materials were sent to the investigators so that preliminary toxicity and range finding tests were limited. Furthermore, no information was provided to the investigators about the solubility and volatility of the materials they were testing and they were encouraged to use standard protocols. Thus, relatively volatile and insoluble compounds like MC would not be likely to give positive responses, especially if they were weak mutagens.

5.3.2.3 Gonadal Effects--Two studies have been reported bearing on the ability of MC to reach germ tissue and cause adverse effects. In the study by Riddle et al. (1981) male and female ICR Swiss mice were given daily doses of 0, 99.4, 2,640, or 8,250 mg/kg MC in the drinking water. It was reported that the oral LD_{50} was about 10,000 mg/kg. The authors reported that no dose-dependent effects were observed on fertility, gestation, viability, or lactation indices, nor were any dose-related effects reported in the F/0 generation. These conclusions cannot be evaluated, however, because they were presented in abstract form without supportive data.

Topham (1980) gave 5 daily i.p. injections of MC purified by J. Ashby of Central Toxicology Laboratory of ICI Ltd., Alderly Park, to groups of 5 (CBA x BALB/c) F_1 male mice. The doses were 0.1, 0.25, 0.5, 1.0, and 2.0 mg/kg. The highest dose was about 0.5 the LD_{50}. Five weeks after the last dose, smears of caudal sperm were coded and examined for head abnormalities. Cyclophosphamide monohydrate (20 mg/kg/day/5 days) and injections of either saline, corn oil, or 0.5% Tween 80 in water were used as concurrent positive and vehicle controls, respectively. MC was reported to be negative in this study. However, because no data were presented these conclusions cannot be assessed.

5.3.2.4 Summary and Conclusions--Because of its volatility and relatively low solubility in water, MC is difficult to test for its mutagenic potential. Care must be taken to ensure the indicator organisms (or appropriate cells in whole animal tests) are exposed to the material in sufficient concentrations to provide an adequate test. Although MC has been tested for gene mutations in *Salmonella* and *Drosophila*, chromosomal mutations in rats and mice, and for its ability to cause adverse effects in mouse testes, most of the experiments are judged to be inadequate because the chemical and physical properties of the compound were not accounted for in the experimental design.

Commerically available MC has been shown to be weakly mutagenic in *Salmonella*, under special treatment conditions, by four different laboratories. Negative responses were reported in other gene mutation tests using yeast, mammalian cells in culture, and *Drosophila* sex-linked recessive lethal tests. However, these test results cannot be interpreted as indicating a lack of mutagenic potential for MC because no precautions were taken to ensure adequate exposure of the test organisms or that sufficiently large test populations were employed.

Chromosomal aberration tests have also been reported to be negative. These tests are also judged to be inadequate because of problems in experimental design (i.e. insuring adequate exposure and generating and scoring a sufficiently large experimental population).

The ability of MC to reach the gonads and cause genotoxic damage has not been adequately assessed either. However, it has been reported to be negative in a dominant lethal assay and a sperm head abnormality assay.

Based on the weight of available evidence it can be concluded that commercially available samples of MC are weakly mutagenic to base-pair substitution strains of Salmonella under treatment conditions where sufficient exposure is ensured. However, the abailable data are inadequate for reaching firm conclusions regarding the ability of MC to cause gene mutations in other organism or other types of genetic damage.

In view of deficiencies in the available information, additional testing in other assays for gene mutations (e.g. yeast, mammalian cells in culture, Drosophila) and other indicators of DNA damage (e.g. sister chromatid exchanges, unscheduled DNA synthesis) is necessary to resolve the issue whether or not MC is a mutagen. Purified samples of MC free of mutagenic substances should be used if it is desired to assess the mutagenicity of this chemical substance per se. Of course, commercial formulations of material should be adequately tested also. Because of MC's physical properties and the data thus far available which indicates it is not a potent mutagen, all additional studies should be appropriately designed to ensure appropriate exposure of the indicator organisms (i.e. prevent excessive evaporation and overcome its low solubility in water).

Because similar positive responses were found in several laboratories with the Salmonella assay, including those testing "purified" samples of MC (but still containing 1-2% unknown contaminants) MC is judged to have mutagenic potential. The possibility that this compound or its metabolites may cause mutagenic effect in humans should be considered.

5.3.3 Evaluation of the Carcinogenicity of Methyl Chloroform

The purpose of this section is to provide an evaluation of the likelihood that MC is a human carcinogen, and, on the assumption that it is a carcinogen, to provide a basis for estimating its public health impact, including a potency evaluation in relation to other carcinogens. The evaluation of carcinogenicity depends heavily on animal bioassays and epidemiologic studies when available.

However, information on mutagenicity and metabolism, particularly in relation to interaction with DNA, and pharmacokinetic behavior, respectively, have an important bearing on the qualitative assessment of carcinogenicity. The available information on these subjects is reviewed in the other sections of this document. This section presents an evaluation of a cell transformation study, animal bioassays dealing with the carcinogenicity of MC and its contaminant, 1,4-dioxane, and finally, a summary and conclusions dealing with all relevant aspects of carcinogenicity.

5.3.3.1 Animal Studies

5.3.3.1.1 Cell transformation study. Price et al. (1978) exposed Fischer rat embryo cell cultures (F1706, subculture 108) to MC liquid at concentrations of 9.9×10^1 and 9.9×10^2 uM for 48 hours. MC was diluted with growth medium to yield the appropriate doses. The MC sample obtained from the Fisher Scientific Company was purportedly $\geq$ 99.9% pure, but a personal communication from Mr. Carlson of the Fisher Scientific Company revealed that the MC (about 95% pure), which was supplied by them to Dr. Price, was really the product of the Dow Chemical Company. The chemical composition of Dow's MC as reported by Quast et al. (1978) of the Dow Chemical Company is given in Table 5-15. The cells were grown in Eagles minimum essential medium in Earle's salts supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 0.1 mM nonessential amino acids, 100 ug penicillin, and 100 ug streptomycin per ml. Quadruplicate cultures were treated at 50% confluency with each dose. After treatment, cells were cultured in growth medium alone at 37°C. Transformation of cells treated with either dose level of MC was observed by 23 and 44 days of incubation and was characterized by progressively growing foci composed of cells lacking contact inhibition and orientation. There was no transformation of cells grown in medium alone or in the presence of a 1:1000 acetone concentration. Fifty-two and 55 microscopic foci per three dishes with low and high MC doses, respectively, were found in dishes inoculated with 50,000 cells from cultures treated four subcultures earlier and held for four weeks at 37°C in a humidified CO_2 incubator prior to staining.

Subcutaneous injection of cells treated with 9.9×10^1 uM 1,1,1-trichloroethane two subcultures earlier produced local fibrosarcomas in 8/8 newborn Fischer 344 rats within 68 days following treatment. The ability of cells grown in growth medium alone to induce local fibrosarcomas was not determined;

TABLE 5-15. COMPOSITION OF THE FORMULATION OF 1,1,1-TRICHLOROETHANE USED IN CHRONIC INHALATION STUDIES IN RATS (Quast et al. 1978)

Compounds*	Liquid volume %	Calculated weight %
1,1,1-Trichloroethane	94.71	95.88
Nitromethane	0.44	0.38
Butylene oxide	0.74	0.46
1,4-Dioxane	3.93	3.11

*Analysis of 1,1,1-trichloroethane Lot TA02013B by gas chromatography.

however, this tumor type did not develop in rats given cells grown in the presence of a 1:1000 concentration of acetone. Exposure of cells to 3.7 x 10^{-1} uM 3-methylcholanthrene produced 124 microscopic foci per three dishes in the inoculation test described above by 37 days of incubation and local fibrosarcoma in 12/12 rats by 27 days following subcutaneous injection of cells. The exposure of 3-methylcholanthrene was attained by initial dilution in acetone to 1 mg/ml followed by further dilution in growth medium to 0.1 ug/ml (personal communication, Dr. Price) (Table 5-16). This study demonstrates that exposure for 48 hours to 95% pure MC (Dow) can transform Fischer rat embryo cells (F1706, 108 passage) in culture. Transformation frequency of the cells are comparable to methyl cholanthrene-treated cells. Furthermore, like methylcholanthrene-transformed cells, the cells transformed by MC were also highly malignant in newborn Fischer 344 rats.

5.3.3.2 Animal Bioassays - Rats--Two rat bioassays have been completed and one is in progress. The completed studies include a National Cancer Institute (NCI) gavage bioassay (1977) and an inhalation study by the Dow Chemical Company (1978). A 2-year carcinogenesis bioassay of MC given by gavage is now underway by the National Toxicology Program (NTP) in mice and rats. The MC being used in this study contains a very low percentage of dioxane. The animals have been sacrificed, and a report is scheduled for completion in late 1982, peer-review in early 1983, and probable release in late 1983.

TABLE 5-16. FISCHER RAT EMBRYO CELL TRANSFORMATION STUDY (F1706,108 Passage)[†]

Chemical	Dose	Duration of Treatment	Average No. of Tumor Foci/5×10^4	Tp = p.c. of Cells Transformed (Growth in Agar)	Tumorigenicity of Cells in Newborn Fischer 344 Rats (Tumor Observed Days Post Inoculation)
MEM (Control)			0	0	
Acetone MEM (negative control)	1:1000	48-hours	0	0	0/13 (8%) 82 days
Methylcholanthrene (positive control)	3.7×10^{-1} uM	48-hours	124	0.24	12/12 (100%) 27 days
1,1,1-Trichloroethane	9.9 x 10uM	48-hours	52	0.104	8/8 (100%) 68 days
1,1,1-Trichloroethane	9.9×10^2 um	48-hours	55	0.11	N.D.[*]

[*] N.D. = not done.

[†] Adapted from Price et al. (1978)

The NCI bioassay (1977) was done with technical grade MC purchased from Aldrich Chemical Company, Inc., Milwaukee, Wisconsin. The purity was checked by Hazleton Laboratories of America, Inc., Vienna, Virginia, using gas-liquid chromatography (glc) and infrared spectrophotometry. Analyses by glc showed that it contained 95% MC and 3% 1,4-dioxane, an inhibitor routinely added to commercial preparations of MC. The remaining 2% of the glc peak area contained several minor impurities, two of which may have been 1,1-dichloroethane and 1,1-dichloroethylene. In this study, Osborne-Mendel rats were treated with 750 mg/kg and 1500 mg/kg MC in corn oil 5 times a week for 78 weeks by gavage (NCI 1977). The rats were observed an additional 32 weeks with the experiment ending at 110 weeks. Both males and females were used with 20 of each sex untreated and 50 of each sex at each dose level.

The study was inadequate because only 3% of the treated rats survived to the end of the experiment. The survival of both sexes of dosed rats was less than that of the matched control groups, which was also inadequate in the males. In male rats, 6/20 (30%) of the controls, 32/50 (64%) of the low-dose group, and 36/50 (72%) of the high-dose group died within a year of the start of the study. The Tarone statistical test of survival showed a dose-related positive trend ($P < 0.001$) in the proportions of deaths over the period of the experiment, although this differential mortality is not reflected in the survival at 78 weeks. In female rats, 1/20 (5%) of the matched controls, 24/50 (45%) of the low-dose group, and 21/50 (42%) of the high-dose group died in the first year. As in male rats, the statistical test for a positive dose-related trend was significant ($P < 0.04$). In both sexes, the early mortality in the MC-treated rats may have reduced the incidence of late-appearing tumors; this is especially true in the males, since none survived to the scheduled termination of the study.

Fewer of the rats receiving MC survived at both 78 and 110 weeks than did the positive control rats receiving the known carcinogen carbon tetrachloride (Table 5-17). A variety of neoplasms (Table 5-18) were observed in the MC-treated groups, but with incidences not statistically different from matched controls. Because of the high mortality in rats, this negative result cannot be used to draw any conclusions regarding the carcinogenicity of MC. The NCI Clearing House on Environmental Carcinogens concluded that the carcinogenicity of MC could not be determined from this study (NCI Clearing House 1977). It should

TABLE 5-17. COMPARISON OF SURVIVAL OF CONTROL GROUPS, 1,1,1-TRICHLOROETHANE-TREATED, AND CARBON TETRACHLORIDE-TREATED (POSITIVE CONTROL) RATS (NCI Bioassay 1977)

	1,1,1-Trichloroethane			Carbon Tetrachloride		
Group	Initial No. of Animals	Number Alive at 78 Weeks	Number Alive at 110 Weeks*	Initial No. of Animals	Number Alive at 78 Weeks	Number Alive at 110 Weeks*
Male						
control	20	7	0	20	20	12
low dose	50	1	0	50	34	15
high dose	50	4	0	50	35	8
Females						
control	20	14	3	20	18	14
low dose	50	9	2	50	38	20
high dose	50	12	1	50	21	14

*Time in study at last weighing.

be noted that the isomer, 1,1,2-trichloroethane, is carcinogenic in mice, inducing liver cancer and pheochromocytomas in both sexes. Dichloroethanes, tetrachloroethanes, and hexachloroethane also produce liver cancer in mice and other types of neoplasms in rats (Table 5-19).

The Dow Chemical Company study (Quast et al. 1978) treated groups of Sprague-Dawley rats by inhalation under conditions that were similar to those experienced by workers (6 hours/day, 5 days/week, over one-half of a lifetime). Rats were treated 12 months and observed until death or until they reached the age of 31 months. Doses of 875 and 1750 ppm were 2.5 and 5 times the threshold limit value of 350 ppm. The composition of the formulation of the MC is given in Table 5-20. The average frequency of tumor occurrence in the treated animals was similar to that of controls (Table 5-21).

TABLE 5-18. STATISTICAL ANALYSES OF THE INCIDENCE OF TUMORS AT SPECIFIC SITES IN MATCHED CONTROLS AND 1,1,1-TRICHLOROETHANE-TREATED RATS (NCI Bioassay 1977)

Topography: Morphology	Males* Matched Control	Males* Low Dose	Males* High Dose	Females* Matched Control	Females* Low Dose	Females* High Dose
Total Animals: All Tumors†	3/20	6/48	6/50	7/20	7/50	9/50
P Values§	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Weeks to first observed tumor	72	28	50	58	64	56
Pituitary: Chromophobe						
Adenoma†	0/20	0/48	0/48	3/20	2/48	1/48
P Values	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Weeks to first observed tumor	---	---	---	---	---	---
Thyroid: Follicular-Cell						
Adenoma†	0/20	0/48	0/50	2/20	0/50	1/49
P Values§	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Weeks to first observed tumor	---	---	---	---	---	---
Adrenal: Cortical						
Adenoma†	0/20	3/49	1/50	2/19	1/48	2/49
P Values§	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Weeks to first observed tumor		28	106	85	99	106

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*Low- and high-dose gruops received 1,1,1-trichloroethane in corn oil by gavage 5 times per week in doses of 750 and 1,500 mg/kg body weight, respectively.

†Number of tumor-bearing animals/number of animals examined at site.

§Beneath the incidence of the matched controls is the probability level for the Armitage test for positive dose-related trend in proportions when it is below 0.10; otherwise, N.S. = not significant. Beneath the dosed group incidence is the probability level for the Fisher Exact (conditional) Test for comparison of that dosed group with the matched control group when it is below 0.10; otherwise, N.S. = not significant.

TABLE 5-19. SUMMARY OF NCI/NTP CHLOROETHANE BIOASSAY RESULTS AS OF 1982

Compound	Species/Sex	Tumor Site	Statistically Significant Tumors
Monochloroethane	No Testing Planned		
1,1-dichloroethane	Retesting recommended because initial results inconclusive		
1,2-dichloroethane	rats/female	mammary gland	adenocarcinomas
1,2-dichloroethane	rats/male	forestomach	squamous cell carcinoma
		circulatory system	hemangiocarcinomas
		subcutaneous tissue	fibromas
	mice/female	mammary gland	adenocarcinomas
		endometrium	stromal sarcomas
		lungs	adenomas
	mice/male	lungs	adenomas
1,1,1-trichloroethane	Draft report in preparation		
1,1,2-trichloroethane	mice/female	liver	hepatocellular carcinomas
	mice/male	liver	hepatocellular carcinomas
	mice/male and female	adrenal glands	pheochromocytomas
1,1,1,2-tetrachloroethane	Final report in preparation		
1,1,1,2-tetrachloroethane	mice/female	liver	hepatocellular carcinomas
	mice/male	liver	hepatocellular carcinomas
pentachloroethane	Final report in preparation		
hexachloroethane	mice/female	liver	hepatocellular carcinomas
	mice/male	liver	hepatocellular carcinomas

TABLE 5-20. AVERAGE FREQUENCY OF TUMOR OCCURRENCES IN RATS TREATED WITH METHYL CHLOROFORM
(Quast et al. 1978)

	Number of Animals		Total Neoplasms/Animal	
	Male	Female	Male	Female
Control	189	189	1.06	2.97
875 ppm	91	92	0.85	2.67
1750 ppm	93	93	1.11	3.23

TABLE 5-21. COMPARISON OF SURVIVAL OF CONTROL GROUPS, 1,1,1-TRICHLOROETHANE-TREATED, AND CARBON TETRACHLORIDE-TREATED (POSITIVE CONTROL) MICE
(NCI Bioassay 1977)

	1,1,1-Trichloroethane			Carbon Tetrachloride		
Group	Initial No. of Animals	Number Alive at 78 Weeks	Number Alive at 90 Weeks	Initial No. of Animals	Number Alive at 78 Weeks	Number Alive at 90 Weeks
Males						
control	20	6	2	20	13	7
low dose	50	21	15	50	11	0
high dose	50	14	11	50	2	1
Females						
control	20	12	11	20	18	17
low dose	50	29	23	50	10	0
high dose	50	14	13	50	3	1

When tumors at each site by tumor type, both benign and malignant, were examined, there were eight differences between control and treated animals at the $P < 0.05$ level (Fisher Exact Probability Test). Seven of these were decreased tumor incidence; one was an increase in ovarian granulosa cell tumors in females at the 875 ppm dose. There were no ovarian tumors in 189 controls; however, there were three in 33 female rats treated at 875 ppm ($P = 0.003$), and two in 82 female rats treated at 1750 ppm ($P = 0.14$). Since ovarian granulosa cell tumors are rare and the P value was low for the animals treated at 875 ppm, it will be of interest to see whether this result is repeated in the NTP study.

The Dow study suffers from two drawbacks: 1) the animals were treated for only 12 months rather than a lifetime, but they were observed for another 12 months, and 2) it is not evident that the maximum tolerated dose was used during the treatment period. There is no evidence that a range-finding study (subchronic) had been done before the start of the experiment. The treated animals in the Dow study did not differ from the untreated animals in body weight, terminal organ weight, or mortality. The only sign of toxicity was an increased incidence of focal hepatocellular alterations in female rats at the highest dosage.

5.3.3.3 Animal Bioassays - Mice--In the NCI bioassay (NCI 1977), B6C3F1 hybrid mice were used with 20 animals of each sex in the control group and 50 animals of each sex at each treatment dose. The time-weighted average doses were 2807 mg/kg and 5615 mg/kg. The mice were treated by gavage 5 days a week for 78 weeks and observed for another 12 weeks for a total of 90 weeks in the experiment.

In male mice, 10/20 (50%) of the matched-control group, 21/50 (42%) of the low-dose group, and 25/50 (50%) of the high-dose group died within a year of the start of the experiment. In female mice, 1/20 (5%) of the matched-control group, 9/50 (18%) of the low-dose group, and 20/50 (40%) of the high-dose group died within the first year of the study. In females, the Tarone test for positive dose-related trend in the proportions surviving had a significance level of $P = 0.002$, although this differential mortality is not reflected in the survival at 78 weeks. Table 5-21 shows that a few mice receiving carbon tetrachloride survived until the planned termination of the test, and 25 to 40% of those treated with MC reached the planned termination date. The high early mortality in mice receiving MC may have lowered the incidence of late-appearing tumors. The treated animals gained less weight than the controls.

A variety of neoplasms (Table 5-22) were observed in MC treated groups, but with incidences not statistically different from matched controls. Because of the high mortality in mice, this negative result cannot be used to draw any conclusions regarding the carcinogenicity of MC.

5.3.3.4 Carcinogenicity of 1,4-Dioxane--Methyl chloroform contains a small amount of stabilizing substances. The concentration of specific stabilizers that had been identified in various commercial MC products is shown below (Aviado 1977 and Detrex 1976, cited by Mazaleski 1979).

	Volume %
Nitromethane	0.4 - 1.8
Butylene oxide	0.4 - 0.8
1,4-Dioxane	2.5 - 3.5
Dioxolane	1.0 - 1.4
Methyl ethyl ketone	1.0 - 1.4
Toluene	1.0 - 1.4
2-Butyl alcohol	0.2 - 0.3
Isobutyl alcohol	1.0 - 1.4

Not all of these stabilizers are in every product, but the maximum total inhibitor package (combinations of stabilizers) appears to be between 7 and 8% by volume (Aviado 1977, cited by Mazaleski 1979).

Since 1,4-dioxane is a contaminant in MC (about 3%), the carcinogenicity of 1,4-dioxane has been studied extensively. The results of these studies are summarized in Table 5-23.

It should be noted that 1,4-dioxane causes liver and nasal tumors in more than one strain of rats and hepatocellular carcinomas in mice. Liver tumors have been induced by dioxane in both male and female rats, as well as in mice. These animal results, coupled with a reported finding of nasal carcinomas in furniture workers exposed to 1,4-dioxane (NCI 1978, p. 108), suggest that 1,4-dioxane is a potential human carcinogen. A detailed evaluation of the carcinogenicity of 1,4-dioxane is currently being prepared by the CAG.

5.3.3.5 Epidemiologic Studies--No epidemiologic studies exist for MC.

5.3.3.6 Potency Estimates--No data exist which can be used to estimate quantitatively the potential human carcinogenicity of MC.

TABLE 5-22. STATISTICAL ANALYSES OF THE INCIDENCE OF TUMORS AT SPECIFIC SITES IN MATCHED CONTROLS AND 1,1,1-TRICHLOROETHANE-TREATED MICE
(NCI Bioassay 1977)

		Males*			Females*	
Topography: Morphology	Matched Control	Low Dose	High Dose	Matched Control	Low Dose	High Dose
Total Animals: All Tumors†	2/15	2/47	6/49	4/18	2/48	3/50
P Values§	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Weeks to first observed tumor	80	89	50	50	54	26
Hematopoietic System: Malignant Lymphoma†	2/15	0/47	2/49	3/18	1/48	0/50
P Values	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Weeks to first observed tumor	80	---	64	80	90	---
Liver: Hepatocellular Adenoma or carcinoma or Neoplastic Nodule†	0/15	0/47	4/49	0/18	0/48	0/50
P Values§	P = 0.035		N.S.	N.S.	N.S.	N.S.
Weeks to first observed tumor	---	---	---	---	---	---

*Low- and high-dose groups received 1,1,1-trichloroethane in corn oil by gavage 5 times per week in time weighted average doses of 2,807 and 5,615 mg/kg body weight, respectively.

†Number of tumor-bearing animals/number of animals examined at site.

§Beneath the incidence of the matched controls is the probability level for the Armitage test for positive dose-related trend in proportions when it is below 0.10; otherwise, N.S. = not significant. Beneath the dosed group incidence is the probability level for the Fisher Exact Test for comparison of that dosed group with the matched control group when it is below 0.10; otherwise, N.S. = not significant.

TABLE 5-23. SUMMARY OF ANIMAL CARCINOGENICITY STUDIES FOR 1,4-DIOXANE

Species	Strain	Route, Frequency of Administration	Sex	Control	Dose	Tumor Type	Reference
Rats	Wistar	In drinking water for 63 weeks	M	Untreated	300 mg/day average	Hepatocellular carcinoma, renal transitional cell carcinoma, myeloid leukemia, and lymphosarcoma	Argus et al. 1965
Rats	Sprague-Dawley derived Charles River CD	In drinking water for 13 months	M	Untreated	0.75, 1.0, 1.40, and 1.80%	Hepatocellular carcinoma (dose-response) 4/30, 9/30 16/30, 23/30	Argus et al. 1973
Guinea pigs		In drinking water for 23 months	M	Untreated	588-635 g in 23 mo.	Gall bladder carcinoma, hepatoma, renal adenoma	Hoch-Ligeti and Argus 1970
Rats	Sprague-Dawley derived Charles River CD	In drinking water for 13 months	M	Untreated	0.75, 1.0, 1.40, and 1.80%	Squamous cell carcinoma (nasal cavity), hepatocellular carcinoma, and fibroma	Hoch-Ligeti et al. 1970
Mice	Swiss Webster	Applied to shaved skin of back 3 times/week for 60 weeks	M F	Acetone Acetone	Unspecified Unspecified	Carcinoma, subcutaneous tumor	King et al. 1973
Rats	Sherman	In drinking water for 2 years	M & F	Untreated	0.01, 0.1, and 1%	Hepatic tumors P = 0.00022 (all types) Hepatocellular P = 0.00033 carcinoma Nasal carcinoma P = 0.054 (these tumors are at the 1% level)	Kociba et al. 1974
Rats	Wistar	Inhalation 7 hrs daily 5 day/week	M & F	Filtered air	111 ppm	No hepatic or nasal carcinomas Reticulum cell sarcoma M 18/150 vs. 37/206 (P < 0.08) F 18/139 vs. 30/207 Found many other types of tumors but not significant	Torkelson et al. 1974
Rats	Osborne-Mendel	In drinking water for 110 weeks	M & F	Untreated	0.5 and 1.0%	Hepatocellular adenoma (P = 0.001) and squamous cell carcinoma of the nasal turbinates (P = 0.008) (both sexes)	NCI Bioassay 1978
Mice	B6C3F1	In drinking water for 98 weeks	M & F	Untreated	0.5 and 1.0%	Hepatocellular carcinoma (P = 0.001) (both sexes)	

5.3.3.7 Summary and Conclusions--There is no adequate basis for the evaluation of the carcinogenicity of MC. A lifetime animal bioassay using both rats and mice, currently in progress under the National Toxicology Program (NTP), is scheduled for completion in late 1982 and subsequent peer-review and public release in 1983. An earlier National Cancer Institute (NCI) study (1977) in rats and mice was inconclusive due to the poor survival of treated animals. An inhalation study in rats by the Dow Chemical Company (1978) showed no evidence of carcinogenicity, but the doses were given for only half of the lifetime of the animals and the highest dose did not appear to be the maximum tolerated dose.

Technical grade methyl chloroform has been shown to be weakly mutagenic and to transform animal cells *in vitro* using Fischer rat embryo cell line F1706. Technical grade methyl chloroform contains about 3% of the stabilizing substance, 1,4-dioxane, which shows evidence of being a carcinogen (Kociba et al., 1974; Argus et al., 1965, 1973; NCI 1978).

Therefore, because of the inconclusive results of the NCI gavage bioassay in rats and mice, the dosage inadequacies in the negative Dow inhalation test, and the possible contribution of dioxane to the positive mutagenic and cell transformation tests, a final judgment on the carcinogenicity of methyl chloroform will have to be deferred until the results of the ongoing NTP bioassay, using methly chloroform which has a very low percentage (0.002%) of 1,4-dioxane, are available.

5.4 SUMMARY OF ADVERSE HEALTH EFFECTS AND LOWEST OBSERVED EFFECTS LEVELS

5.4.1 Inhalation Exposure

The high volatility of methyl chloroform (MC), the extensive use of this compound as an industrial solvent, and the early interest in MC as an anesthetic has resulted in many reports in the scientific literature of human exposure to MC. Human experimental studies using acute and subchronic exposures have been performed using a few clinical-level tests of motor and cognitive performance. In many cases, these studies were poorly documented and studied only a few subjects using non-conservative statistics, where statistics were used at all. No studies using sensitive tests of cognitive performance or tests of vigilance or sensory function were found. While information on human chronic inhalation exposure to MC is available from studies of occupationally exposed groups, there is uncertainty in these studies as to the exact extent of exposure; some studies are complicated by simultaneous exposure to other chemicals used in the workplace. Although these human studies have deficiencies which preclude any individual study from being used for human risk assessment, the combined information presented in these studies can be used to estimate approximate dose-response relationships which provide a relatively clear description of the toxic effects of MC. However, because no quantitive studies or sensitive dependent variables were studied, no definitive conclusions about the effects of human exposure of MC can be drawn at this time.

Studies in experimental animals are available for acute and subchronic exposure to MC, but the uncertainty of extrapolation from animals to humans makes this animal data useful only in a supportive role for human risk assessment.

5.4.1.1 Effects of Single Exposures--Lethal effects of acute exposure to MC have been reported after accidental exposure and abuse, with death resulting from CNS depression followed by respiratory and cardiac failure (Hall and Hine, 1966; Bas, 1970; Stahl et al., 1969; Bonventre et al., 1977; Klienfeld and Feiner, 1966; Hatfield and Maykoski, 1970; Caplan et al., 1976). From the levels of MC in the blood and brain of cadavers, estimates have been made of the concentration of MC present in the air during the time the victim was exposed. These estimates range from 200 to 102,900 ppm (1,080 to 555, 660 mg/m^3), with the majority of values being between 6,700 and 18,600 ppm (36,180 and 100,440 mg/m^3) (Table 5-24). However, these estimates are extremely crude and probably low since it is not known to what degree the MC had dissipated from the victims' bodies prior to obtaining tissue samples. Also, some of the observed deaths which occurred at relatively low MC concentrations may have resulted from aspiration pneumonia prior to extensive involvement of the CNS. A clearer indication of the levels of MC needed to produce narcosis is available in the study of Dornette and Jones (1960) investigating the use of MC as an anesthetic in humans. Although this study gives an indication of the levels of MC which cause CNS depression, presumably a higher concentration would be needed to cause depression severe enough to result in respiratory or cardiac failure. From these data and the LC_{50} concentrations of 14,250 ppm (75,950 mg/m^3) obtained by Adams et al. (1950) for rats, it can be estimated that a single short-term exposure to as much as 5,000 ppm (27,000 mg/m^3) would not be expected to be lethal; exposure to higher concentrations and longer duration of exposure, however, could produce narcosis and possibly death.

TABLE 5-24. HUMAN FATALITIES ASSOCIATED WITH METHYL CHLOROFORM

Case No.	Sex	Material or Product Inhaled	Condition of Lungs at Autopsy	1,1,1-Trichloroethane Concentrations		Remarks	Source
				Blood mg%	Air ppm^x		
1	F	Energine	passive congestion	72	102,900		Hall and Hine, 1966
2	M	1,1,1-trichloroethane	no autopsy	--	--	75,000 ppm in work space; collapsed after leaving work area	Kleinfeld and Feiner, 1966
3	M	"degreaser"	acute congestion and edema	30.0	42,900		Bonventre et al., 1977
4	M	Chlorothene®	heavy, edematous	13	18,600	possible aspiration, pneumonia	Hall and Hine, 1966
5	M	1,1,1-trichloroethane	heavy, edematous	12.0	17,000		Stahl et al., 1969
6	M	"	heavy, edematous	6.3*	9,000		Stahl et al., 1969
7	M	"	heavy, edematous	6.2	8,900		Stahl et al., 1969
8	M	"	heavy, edematous	6.0	8,600		Stahl et al., 1969
9	M	"	moderately edematous	6.0	8,600		Hatfield and Maykoski, 1970
10	M	"paint remover"	moderately edematous	4.7*	6,700		Stahl et al., 1969
11	F	"paint remover"	acute edema & congestion	2.0	2,900	ethanol conc. in blood was 0.04%	Caplan et al., 1976
12	M	1,1,1-trichloroethane	markedly edematous	0.15	200	possible aspiration, pneumonia	Stahl et al., 1969

[x] Calculations based on assumption from Stewart et al., 1969, of one hour exposure correlating to 0.07 mg percent in blood per 100 ppm in air.

[*] Estimated from brain concentration.

TABLE 5-25. NON-LETHAL EFFECTS OF METHYL CHLOROFORM ON HUMANS

Study	Dose/Species	Effect
Dornette & Jones, 1960	10,000-26,000 ppm 6,000-22,500	Induction of anesthesia Maintain light anesthesia Depressed BP during mod. anesthesia Tendency to develop ventricular arrhythmias during hypoxia (reversed by oxygenation)
Siebecker et al., 1960	Anesthesia	Little change in EEG-similar to halothane anesthesia
Stewart et al., 1961	0-2,650 ppm for 15 min	See Table 5-1
	500 ppm	No effects
	900-1000 ppm	See Table 5-2
Torkelson et al., 1958	900-1000 ppm for 75 min	Slight eye irritation and lightheadedness; Flanagan and Rombert test showed slight loss of coordination and equilibrium
	1,900 ppm for 5 min	Equilibrium disturbed, positive Romberg test
Torkelson et al., 1958 Stewart, 1968; 1971 Am. Ind. Hyg. Assoc.	Results of single exposures	See Table 5-7
Stewart et al., 1969	500 ppm 6.5-7 hr/day for 5 days	Mild subjective complaints; abnormal Romberg
Stewart et al., 1975	500 ppm	See Table 5-3

TABLE 5-25. (continued)

Study	Dose/Species	Effect
Gamborale and Hultengren, 1973	250, 350, 450, 550 ppm for 4-30 min periods	Change in manual dexterity and perceptual tests in exp. vs. control groups
Salvini et al., 1971	450 ppm for 2-4 hr periods	Decreased perceptive capability under stress, eye irritation
Maroni et al., 1977	110-990 ppm	No effects
Seki et al., 1975	4, 25, 28, 53 ppm	No effects
Kramer et al., 1978	11-838 ppm → x = 115	No effects, although SGPT and albumin were different in exposed vs. control group.
Stewart and Andrews, 1966 Stewart, 1971 Litt & Cohen, 1969		See Table 5-4

The effects of exposure of human volunteers to MC for single short term periods were reported for MC levels far below the levels which cause narcosis (Table 5-25). Stewart et al. (1961) exposed 7 subjects to vapors of MC which were increased from 0 to 2,600 ppm (0 to 14,040 mg/m^3) in increments of 15 minutes each. The progress of observed effects is presented in Table 5-1, with 6 of 7 subjects complaining of throat irritation at 1,900 ppm (10,260 mg/m^3). The progressive exposure method used in this study and the small number of subjects makes the results difficult to interpret. However, in a second experiment in which subjects were exposed to 900 ppm (4,860 mg/m^3) MC for periods of 20, 35, or 73 minutes, difficulty was observed in the performance of the Romberg tests, and some lightheadedness was experienced. No effects were observed in subjects exposed to 500 ppm (2,700 mg/m^3) for MC for 78 or 186 minutes. In both of these experiments, commercial grade MC was used which contained the inhibitors dioxane (2.4-3.0%), butanol (0.12-0.3%) and small amounts of 1,2-dichloroethane. These compounds may have also had some effect on the subjects. In support of the above findings, Torkelson et al. (1958) obtained similar results with 2 groups of 4 subjects each exposed to 500 or 900 ppm (2,700 or 4,860 mg/m^3) of pure MC for 75 to 90 minutes. Subtle changes in perceptive capability were observed following exposure to 350 and 450 ppm (1,890 and 2,430 mg/m^3) MC by Gamborale and Haltengren (1973) and Salvini et al. (1971). However, these last two observations are questionable since the effects of menthol used to mask the odor of MC in the first study were not evaluated, and in the second study the control subjects were not matched for all intervening variables such as food and drinking habits. Since the above-mentioned studies were largely qualitative and since only gross dependent variables were observed, conclusions are tentative at best.

Although a precise dose-response gradient of effects produced by MC exposure cannot be derived, it is possible to establish a crude relationship between exposure and effects from a compilation of the human data available. A summary of the estimated dose-response relationships for acute effects of single short-term exposures is presented below:

>5,000 ppm	Onset of narcosis
1,900-2,650 ppm	Lightheadedness, irritation of the throat
1,000 ppm	Disturbance of equilibrium
350-500 ppm	Slight changes in perception, obvious odor
100 ppm	Apparent odor threshold

The approximate concentrations of MC which elicit a particular adverse effect have greater uncertainty at the two extremes, that is, at levels greater than 10,000 ppm (270,000 mg/m^3), and the no-observed-adverse-effect level (NOEL)*, 350-500 ppm (1,890 to 2,700 mg/m^3). This results from the inherent difficulties in obtaining exact exposure values in the cases of accidental overexposure to MC, and the difficulty in the acquisition of either quantitative or qualitative data on slight behavioral changes at the lower exposure levels. Acute overexposure to MC may be limited by the low odor threshold in humans of

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*NOEL: is defined as the exposure level at which there are no statistically significant increases in frequency or severity of effects between the exposed population and its appropriate control.

100 ppm (540 mg/m^3). Others report that an obvious odor is present at 500 ppm (2,700 mg/m^3). It also should be noted that there are no reports of residual adverse effects from a single exposure to MC.

A major uncertainty in the dose-response relationship estimated for MC from the compilation of the available human reports is the lack of information on the length of exposure in accidental exposure, and the short duration (less than 2 hours) in most of the studies in which controlled exposures of human volunteers were used. Although inhaled MC is retained in the lungs in proportion to the concentration in the air, the time to reach pulmonary steady-state conditions is relatively long (4 hours). Since the maximum body burden from a given exposure to MC was probably not reached in any of these studies, it is likely that exposures for longer times would result in a greater body burden and more severe effects at a given concentration. In the studies of the inhalation toxicity of MC, there are insufficient data to predict the results of the increased body burden of MC obtained by extending the exposure until steady-state conditions are obtained. However, from the pharmacokinetic data presented in Figure 4-1, it can be reasonably concluded that the effects observed in the dose-response table would not shift by more than 30 percent. From the above discussion, it should be evident that these approximations are crude estimates and contain several areas of uncertainty.

5.4.1.2. Effects of Intermittent or Prolonged Exposures

There is a substantial amount of information from animal studies on the effects of subchronic or chronic inhalation exposure to MC. There is also a lifetime chronic study in rats. As discussed below, the only experimental study of humans involved repeated exposure to MC 5 days per week for 3 weeks and is of such a short duration that no information can be extrapolated from this study as to the long-term effects of MC exposure (Stewart et al., 1976). Observations of occupationally exposed workers exposed up to 6 years at MC levels (TWA) ranging from 50 to 249 ppm (270 to 1,345 mg/m^3) showed no difference between exposed and comparable control populations.

There are, however, three subchronic experimental animal studies with exposures continuing up to 180 days which provide some information on the effects of repeated exposures to MC. The study of Torkelson et al. (1958) using rats, guinea pigs, rabbits, and monkeys, and the study of Eben and Kimmerle (1974) using rats established a no observed effect level (NOEL) for subchronic exposure to MC for 7 to 8 hours a day, 5 days per week for 3 months at 500 and 440 ppm (2,700 and 2,376 mg/m^3), respectively. Similarly, a NOEL of 370 ppm (1,898 mg/m^3) was obtained by Pendergast et al. (1967) in a variety of species (15 guinea pigs, 3 squirrel monkeys, 3 New Zealand rabbits, and 2 beagle dogs) exposed continuously to MC for 6 weeks. In this study there were 3 deaths in the low exposure group (135 ppm; 729 mg/m^3), but these were attributed to lung infections. These three studies would indicate that subchronic exposure to MC in the range of 370 to 500 ppm (1,898 to 2,700 mg/m^3) produces no gross signs of toxicity. However, the report of McNutt et al. (1975) indicates that exposure below this range may alter some biochemical parameters in the liver and brain.

McNutt et al. (1975) observed mild to minimal alterations in the rough endoplasmic reticulum, detachment of polyribosomes, microbodies, and triglyceride droplets in the livers of mice exposed to 250 ppm of MC continuously for 24 weeks. At 1000 ppm (5,400 mg/m^3), the extent of these changes had increased and some individual hepatocyte necrosis was observed. Although it is unclear whether the early biochemical and histologic changes observed at exposures of 250 ppm (1,350 mg/m^3) adversely affected liver function, they may represent the first stages in the sequence of events which leads to the hepatocellular necrosis observed at 1000 ppm (5,400 mg/m^3). The NOEL of 370 to 500 ppm (1,898 to 2,700 mg/m^3) discussed previously may reflect the insensitivity of the parameters investigated in the other studies.

The only study involving multiple experimental exposures of humans was that of Stewart et al. (1975), in which 20 subjects were exposed to 500 ppm (2,700 mg/m^3) of MC for 7.5 hours a day, 5 days per week for 3 weeks. There were no effects on the clinical chemistry of the blood or urine, nor on pulmonary function tests. However, the female subjects did have an increased number of complaints of odor. The authors stated that there was a lack of sleepiness and fatigue which had been reported in a previous study. Again, these tests are not known to be sensitive enough to detect the slight changes in the liver observed in mice at exposures to 250 or 1000 ppm (1,350 or 5,400 mg/m^3) by McNutt et al. (1975). The combined evidence from the human and animal studies would indicate that only minimal effects are produced by continuous exposure to 250 ppm (1,350 mg/m^3) of MC and that the pathologic importance of these effects are unknown.

The studies of Maroni et al. (1977), Seki et al. (1975) and Kramer et al. (1978) reported a NOEL for workers occupationally exposed to MC as high as 350 ppm (1,890 mg/m^3). The short duration of exposure, averaging less than 1 year, of the work population in the report of Kramer et al. (1978) precludes the use of this study in human risk assessment. The study of Seki et al. (1975) provides information on 196 male workers exposed to MC for at least 5 years at concentrations of 4, 25, 28, and 53 ppm (22, 135, 151, and 286 mg/m^3). The number of workers exposed at each concentration was relatively small, with only 42 people exposed to the highest concentration. While no dose related effects were observed, the exposed groups were only compared among themselves and not with a control population. The reported details of the analytical procedures were insufficient to determine whether the analytical data represented measurements over the entire time period (5 years) of exposure of the study population, or whether the concentrations reported were the concentrations in the breathing zone. Most of the deficiences in this study would probably result in an underestimation of the exposure levels. Thus, it is difficult to ascertain any NOEL from this study. Maroni et al. (1977) looked for neurophysiological abnormalities in a population of 21 women who had been exposed for 6.5 years to an average concentration of MC between 110 and 345 ppm (594 and 1,863 mg/m^3). No neurotoxicity was observed in exposed workers, as compared to a control population of 7 unexposed women. The small size of the exposed and control populations, and the limited number of physiological measurements made makes the apparent NOEL from this study extremely uncertain.

5.4.2 Oral Exposure

There is little information on the toxicity of MC by the oral route. As summarized in Table 5-5, the acute LD_{50} for MC has been determined in rats, mice, guinea pigs, and rabbits by Torkelson et al. (1958) and the values range from 8,600 to 14,300 mg/kg body weight. These LD_{50} values could theoretically be used to calculate an approximate human lethal dose using the cubed root of the body weight ratios for interspecies conversion (U.S. EPA, 1980; Freireich et al., 1966; Rall, 1969). However, the data obtained from the species studied in the report of Torkelson et al. (1958) do not show a relationship between MC toxicity and body weight. Therefore, without further information, it would not be justified to place much reliance on an approximate human lethal dose calculated using the above approach. However, as a crude indication of a lethal oral dose of MC, the values were calculated from each species with the range for a human lethal dose falling between 770 and 3940 mg of MC/kg. Also, there is no information from human exposure to MC to indicate whether values obtained from a calculated lethal dose are applicable to human toxicology. For the above reasons it is considered inappropriate to attempt to predict an approximate human lethal dose from the present data available.

There are subchronic studies on oral exposure to MC, and only one chronic study, an NCI bioassay. In the NCI (1977) bioassay, rats and mice were treated by gavage with MC in corn oil 5 days/week for 78 weeks at a level of 750 and 1500 mg/kg body weight for the low and high dose group rats, and 2807 and 5615 mg/kg body weight for the low and high dose group mice. Early deaths were observed in both rats and mice, with a statistically significant dose-related trend observed in male and female rats, and in female mice. The control animals also had poor survival and the early mortality in this group would suggest that MC contributed only partly to the early deaths of the treated animals. Another difficulty with this study is that treatment of animals by gavage is not identical to exposure through food or water since the daily dose of the compound is administered at a single time, resulting in high body levels immediately after treatment. As a result of the poor survival of the control animals and the inappropriateness of the route of administration, the relevance of this study to human risk assessment is questionable.

5.4.3 Dermal Exposure

There is insufficient information available for quantitative risk assessment of dermal exposure to MC. The pharmacokinetic data of Fakabori et al. (1976, 1977) would indicate that absorption of MC through intact skin can contribute significantly to the levels of MC in the body. The extent of dermal absorption was estimated to be 5 percent of respiratory absorption in humans in direct contact with the liquid. The high vapor pressure of MC would preclude dermal contact with this solvent for sufficient periods of time to allow toxic quantities to be absorbed, except in some industrial situations. Even so, the greater efficiency of absorption by inhalation would make this the route of greatest concern.

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